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REVIEW

Cancer and autoimmunity: autoimmune and rheumatic features in patients with malignancies

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Abstract

Objectives—To review the autoimmune and rheumatic manifestations of patients with malignancy.

Methods—A Medline search of all published papers using keywords related to malignancies, autoimmunity, rheumatic diseases, and paraneoplastic syndromes.

Results—Patients with malignant diseases may develop autoimmune phenomena and rheumatic diseases as a result of (a) generation of autoantibodies against various autoantigens, including oncoproteins (P185, 1-myc, c-myc, c-myb), tumour suppression genes (P53), proliferation associated antigens (cyclin A, B1, D1, E; CENP-F; CDK, U3-RNP), onconeural antigens (Hu, Yo, Ri, Tr), cancer/testis antigens (MAGE, GAGE, BAGE, SSX, ESO, SCP, CT7), and rheumatic disease associated antigens (RNP, Sm). The clinical significance of the various autoantibodies is not clear. Anti-oncoprotein and anti-tumour suppression gene antigens are detected before the diagnosis of the cancer or in the early stages of the malignant disease, suggesting a potential diagnostic or prognostic role. Anti-onconeural antibodies are pathogenic and are associated with specific clinical neurological syndromes (anti-Hu syndrome and others). (b) Paraneoplastic syndromes, a wide range of clinical syndromes, including classic autoimmune rheumatic diseases that develop among patients with cancer. (c) Rheumatism after chemotherapy, a clinical entity characterised by the development of musculoskeletal symptoms after combination chemotherapy for malignancy.

Conclusion—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.

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Several studies have indicated a link between rheumatic diseases, autoimmune phenomena, and cancers. An increased risk of haematological malignancies, compared with the general population, was found among patients with rheumatoid arthritis and systemic lupus erythematosus (SLE).^{1,2} Similarly, the prevalence of solid tumours among patients with systemic sclerosis (SSc) is between 3 and 7%.³ In a previous study we reviewed the occurrence of malignancies among patients with various rheumatic and autoimmune diseases.^{2,3} The bi-directional relation between autoimmune conditions and cancer has been recently summarised.⁴

Patients with malignancies may develop autoimmune and rheumatic manifestations. Those features may be the result of generation of autoantibodies, paraneoplastic syndromes, direct invasion of joints and muscles by the tumour cells, or combination chemotherapy. In this paper we review the autoimmune and rheumatic features of patients with solid and haematological malignancies.

Autoantibodies in patients with cancer

Malignant diseases are associated with the induction of autoimmunity that is characterised by the generation of autoantibodies against a wide range of autoantigens.^{5,6} Autoantibody activity has been identified in the sera of patients with solid tumours and in the sera of patients with haematological malignancies. The anti-tumour immune response may result in elicitation of autoantibodies against various autoantigens, including self antigens expressed in tumour cells—a large group of autoantigens

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Table 1 Autoantigens that may induce autoantibody secretion among patients with malignancies

Autoantigen	Characteristics of autoantigen	Autoantibody	References
Oncoproteins	Proteins encoded by oncogenes which play a part in the control of cell growth	Anti-HER-2/neu	6, 17
Tumour suppressor gene proteins	Proteins encoded by tumour suppressor genes, expressed in normal tissues	Anti-P53	19–26
Proliferation associated antigens	Nuclear and cytoplasmic antigens associated with cell cycle regulation and mitosis	Anti-cyclin B1, anti-cyclin A, anti-CENP-F	28–32
Onconeural antigens	Antigens normally found in the nervous system, may be expressed by malignant cells	Anti-Hu, Anti-Yo	37, 39
Cancer/testis antigens	Normally found in testis and expressed in various malignancies	Anti-NY-ESO-1, anti-MAGE-1	45, 46
Autoimmune rheumatic diseases	Normal nuclear and cytoplasmic antigens	ANA, anti-NDA, anti-Sm	47

designated as tumour associated autoantigens.^{6,7}

During the past decade new techniques have been developed to identify various oncoproteins and glycoproteins. More than 400 autoantigens have been identified by the new methodology called SEREX (serological analysis of recombinant cDNA expression libraries of human tumours with autologous serum).⁸

Tumour associated autoantibodies bind:

- Tissue-specific antigens, including tyrosine, actin, galectin-4, and gp75⁹⁻¹⁰
- Membrane receptors such as HER-2/neu oncoprotein⁶
- Tissue restricted antigens, such as MAGE and NY-ESO-1⁷
- Nuclear proteins such as P53,¹¹ c-myc,¹² c-myb,¹³ DNA topoisomerase II,¹⁴ CENP-F,¹⁵ and the nucleolar proteins NOR-90/UBF, fibrillarlin, and B23.¹⁶

Table 1 shows various autoantigens that may trigger the generation of autoantibodies among patients with cancer.

ANTI-ONCOPROTEIN ANTIBODIES

Oncoproteins are proteins encoded by oncogenes or by tumour suppressor genes, or both, and play a part in the control of cell growth and differentiation. Mutation or inappropriate expression of oncoproteins may result in the genesis of malignant diseases. Up to 50% of the sera of patients with breast cancer bind the P185 oncoprotein. This protein is the product of the overexpression of the HER/neu oncogene and it is a trans-membrane protein which is highly similar to the epidermal growth factor receptor. Higher titres of anti-P185 are seen in the early stages of the malignant disease, but they may also be detected in healthy volunteers.¹⁷ Patients with colon cancer develop antibodies that react with the P21 protein, a GTP binding protein. Autoantibody activity against other oncoproteins is seen in the sera of patients with breast, lung, colon, and ovarian tumours. This includes activity against c-myc, c-myb, and l-myc antigens.^{12, 13, 18} Whereas anti-l-myc is detected only in the sera of patients with cancer, anti-c-myc and anti-c-myb are not specific for patients with cancer and they may be found in healthy volunteers and in the sera of patients with SLE.^{12, 13} The clinical significance of the detection of autoantibody activity against oncoproteins is not clear. Further studies are needed to determine whether those autoantibodies have a diagnostic value, prognostic significance and/or, if they can be used to monitor response to specific anticancer treatment.

ANTI-TUMOUR SUPPRESSION GENES

P53 is among the most widely studied tumour suppressor protein.¹⁹ Its role is to prevent carcinogenic and teratogenic lesions. It has been shown that P53 may become immunogenic among patients with malignancy.²⁰

Anti-P53 antibodies have been detected in 3–65% of sera of patients with cancer.^{21, 22} Furthermore, anti-P53 may develop months to years before the clinical diagnosis of cancer.²³ Anti-P53 antibodies were found in the sera of workers exposed to vinyl chloride who developed angiosarcoma²⁴ of the liver and in the sera of heavy smokers who developed lung cancer. The anti-P53 antibody was detected in the sera of the patients before the diagnosis of the malignant disease.²⁵ In another study^{5, 26} anti-P53 was examined in the sera of healthy uranium miners, miners with lung cancer or abnormal chest radiographs, miners with SLE, and healthy controls. Anti-P53 was found in 18% of the sera of miners with lung cancer before the diagnosis of the cancer. The autoantibody was identified in 13% of miners with probable lung cancer, in 14% of miners with SLE or SSc, and in 7.8% of healthy miners. None of patients with SLE who were not miners, or healthy women aged 18–62, had anti-P53 activity in their sera.

In a recent study anti-P53 was reported in 25% of the sera of women with ovarian cancer, and its presence in ascetic fluid was found to be a poor prognostic sign.²⁷

Taken together,²² the data suggest that anti-P53 is found mainly in the sera of patients with cancer. It is generated as a result of a self immunisation process due to the strong immunogenicity of the P53 protein, and it is associated with the P53 gene missense mutation. It has a specificity of 96% and it may be used to detect early carcinoma among patients who are at high risk for developing malignancy.

ANTI-PROLIFERATION ASSOCIATED ANTIGENS

Patients with malignant diseases may generate antibodies reacting with antigens which play a part in cell cycle regulation and mitosis. This includes antibodies against nuclear and cytoplasmic antigens associated with splicing processes and ribosome biosynthesis. Cyclin B1, cyclin A, and cyclin-dependent kinase 2 (CDK) are a group of cell cycle regulating proteins acting at different stages of the cell cycle progression. Overexpression of cyclin E, and cyclin D1 has been noted in cells from patients with squamous cell carcinoma of the lung and in cells of patients with atypia and dysplasia of

the bronchial cells. No expression of cyclin E or cyclin D1 was found in normal bronchial cells.²⁸

The overall frequency of mitosis related autoantibodies was found to be 2% among the sera of 1438 patients with various cancers.⁵ Antibodies reacting with cyclin B1, cyclin A, and CDK were found in 15%, 1%, and 1% respectively of the sera of patients with hepatocellular carcinoma.²⁹ Anti-cyclin B1 was also detected in the sera of patients with chronic active hepatitis and cirrhosis.

Patients with cancer may generate new cell cycle-specific DNA binding nuclear antigens. Sera of patients with lung cancer were found to react with a new antigen designated SG2NA (S/G2 nuclear antigen). This antigen belongs to the transducin-like enhancer of split (TLE) protein family that has a role in regulating nuclear functions associated with the cell cycle.³⁰

CENP-F, also known as P330 and mitosin, is expressed predominantly during G2 and mitosis. It has a role in centromere/kinetochore maturation, chromosome alignment and segregation, regulation of the metaphase checkpoint, anaphase spindle stabilisation, and cytokinesis.³¹

Anti-CENP-F antibodies were found to be associated with cancers. Of 36 patients with anti-CENP-F antibodies, 22 were found to have malignant diseases. Breast and lung cancers were the most common malignancies. The mean titre of the anti-CENP-F antibody among the patients with cancer was 1/10 000 compared with 1/3000 among the group without cancer, indicating a vigorous immune response to CENP-F among patients with malignancies. However, the overall frequency of anti-CENP-F among patients with various malignancies is less than 1%.^{15 32}

Sera of patients with cancers may react with antigens associated with splicing processes and ribosome biosynthesis.¹⁶ Sera from patients with hepatoma may bind the human upstream binding factor (NOR-90/hUBF), the U3-RNP associated fibrillarin, and protein B23, proteins which play a part in ribosome biosynthesis.^{16 33} Antibodies that bind an autoantigen with splicing factor motifs (HCC1) were found in the sera of patients with liver cirrhosis who developed hepatoma,³⁴ suggesting that various proteins involved in mRNA splicing may be antigenic targets in patients with hepatoma.

Table 2 Anti-onconeural antibodies and their clinical significance

Autoantibody	Cancer association	Clinical significance	Reference
Anti-Hu	Small cell lung cancer	Encephalomyelitis Acute sensory or autonomic neuropathy Neuromyotonia	37-39, 75
Anti-VGCC	Small cell lung cancer	Lambert-Eaton myasthenic syndrome	76, 77
Anti-amphiphysin	Small cell lung cancer Breast cancer Thymoma	Stiff man syndrome	79
Anti-Yo	Breast cancer Ovarian cancer Small cell lung cancer	Cerebellar degeneration	40, 41
Anti-Ri	Breast cancer Ovarian cancer Small cell lung cancer	Myoclonous Cerebellar degeneration	40, 42
Anti-Tr	Hodgkin's disease	Cerebellar degeneration	43, 44

AUTOANTIBODIES TO ONCONEURAL ANTIGENS

Onconeural antigens are normally identified in the nervous system, but they may be expressed in malignant diseases by gene activation or depression (table 2). The generation of anti-onconeural antibodies among patients with malignant diseases may result in the development of paraneoplastic neurological syndromes.^{35 36}

Hu antigens are 35-40 kDa, expressed in neurons, and constitute a family of RNA binding proteins characterised by an RNA recognition motif of 80 amino acids.³⁷ The antigen is also expressed in cells from patients with small cell lung cancer (SCLC). Anti-Hu antibodies have been detected in 90% of patients with SCLC and have been associated with encephalomyelitis, sensory neuropathy, cerebellar degeneration, and dysmotility of the gastrointestinal system, a clinical entity designated as the "anti-Hu syndrome".^{38 39}

A high percentage of sera from patients with breast or gynaecological cancers binds another onconeural antigen, designated Yo, which is expressed in the cytoplasm of cerebellar Purkinje cells and in the malignant cells. Three types of the Yo antigen have been identified (cdr 34, cdr 62-1, cdr 62-2) and their corresponding genes are clones. Antibodies reacting with the Yo antigen have been associated with the development of cerebellar degeneration: a clinical syndrome characterised by ataxia, dysarthria, and dysphagia.^{40 41}

Anti-Ri is another anti-onconeural antibody that has been isolated from the sera of patients with breast, SCLC, gynaecological, and other cancers. It binds neuron-specific RNA nuclear proteins with a molecular weight of 55-80 kDa. Cerebellar degeneration and myoclonus have been associated with the anti-Ri antibodies.^{40 42}

Sera of patients with Hodgkin's disease and cerebellar degeneration react with the Tr antigen, a new onconeural antigen localised in the Purkinje cells.^{43 44}

ANTI-CANCER/TESTIS ANTIGEN ANTIBODIES

Cancer/testis antigens refer to a large group of antigens expressed in various tumours. Seven cancer/testis antigens have been identified and they were found to belong to the following gene families: MAGE, GAGE, BAGE, SSX, ESO, SCP, CT7. The ESO family expresses NY-ESO-1, and antibodies reacting with these antigens were found in the sera of patients with melanoma (9.4%), ovarian cancer (12.5%), lung cancer (4.2%), and breast cancer (7.7%). A low frequency (<5%) of anti-MAGE-1 and SSX2 antibodies was found in the sera of patients with melanoma, ovarian, or lung cancer.^{45 46}

AUTOIMMUNE RHEUMATIC DISEASES ASSOCIATED AUTOANTIBODIES

Antinuclear autoantibodies are detected in the sera of patients with cancers. Sera of patients with malignancies were found to bind antinuclear autoantibodies, DNA, histones, Ro, La, Sm, and RNP. Similarly, rheumatoid factor and antiphospholipid autoantibodies (aPL) were

also found in the sera of patients with cancer.^{47, 48}

Raised levels of aPL were found in patients with thrombosis associated with malignancy. The frequency of aPL among patients with cancer varies. In one study 22% of the sera of patients with cancer were aPL positive compared with 3% of healthy controls. A twofold increased risk for thrombosis was found among aPL positive patients with cancer compared with aPL negative patients with cancer.⁴⁹ Lupus anticoagulant activity was reported in 2–12% of the sera of patients with cancer.⁵⁰ Patients with aPL were found to have an increased risk for cancer. In a five year follow up study of 360 aPL positive patients, five patients developed cancer. These included four cases of non-Hodgkin lymphoma.⁵¹

A high proportion of the sera of patients with haematological malignancies binds a large number of autoantibodies. Sera of patients with multiple myeloma, macroglobulinaemia, and chronic lymphocytic leukaemia have rheumatoid factor activity and bind DNA, myelin associated glycoproteins, and other autoantigens. This autoantibody activity is the result of malignant transformation of B cells that produce autoantibodies.^{52, 53}

Autoantibodies from patients with haematological malignancies have the characteristics of natural autoantibodies (NAA). NAA are self reacting serum antibodies that do not require antigenic stimuli for their production. They are generated by CD5+ B cells, mainly IgM, encoded by germline genes, and are characterised by their low affinity to bind a wide range of self and non-self antigens.⁵⁴

NAA represent a substantial proportion of circulating normal immunoglobulins. Most NAA can react with three or more self or foreign antigens and they play an active part in the preservation and perpetuation of the normal balanced immune response. NAA have a biological role, by which they bind defective self antigens and accelerate their opsonisation and phagocytosis.

NAA are often present in high titres in the sera of patients with viral, bacterial, and parasitic infections, in patients with autoimmune diseases, and in patients with malignancies. High titres of NAA are present in the sera of patients with haematological malignancies, including multiple myeloma, Waldenström's macroglobulinaemia, chronic lymphocytic leukaemia, and B cell lymphoma. Monoclonal antibodies derived from patients with haematological malignancies were found to bind DNA, Sm, RNP, Ro, La, I-Ag, histones, actin, myosin, and others.^{52–55}

Pathogenic IgG autoantibodies were also detected in the sera of patients with haematological malignancies. Autoimmune thrombocytopenia, Sjögren's syndrome, autoimmune haemolytic anaemia, rheumatoid arthritis, SLE, and autoimmune thyroid diseases were all reported among patients with haematological malignancies.⁵⁵

Paraneoplastic autoimmune syndromes

Paraneoplastic syndromes represent a wide range of clinical syndromes that develop among patients with cancers. About 7–10% of patients with cancer develop one of the paraneoplastic syndromes. These may be the result of secretion of various hormones and hormone-like peptide by tumour cells or the result of activation of autoimmune phenomena.⁵⁶ Cushing's syndrome and hypercalcaemia may develop as a result of ectopic secretion of adrenocorticotrophic hormone and parathyroid hormone related proteins. Other hormones that may be secreted by tumour cells include insulin-like growth factors, antidiuretic hormone, growth hormone-releasing hormone, erythropoietin, and others.⁵⁷

Activation of autoimmune mechanisms among patients with cancer may be associated with the development of autoimmune rheumatic diseases. Patients with various rheumatic diseases, including dermatomyositis, polymyositis, vasculitis, and scleroderma, have an increased risk for the development of cancers. However, in a significant number of patients, the malignant disease is diagnosed months or years before the presentation of the rheumatic diseases.

Dermatomyositis is strongly associated with malignancy. Inflammatory myopathy of the proximal muscles and involvement of the skin and internal organs, including lungs, heart, and gastrointestinal system, characterise this disease. Malignant disease is diagnosed in about 25% of patients with dermatomyositis with disease onset above the age of 50. Cancer usually develops within two years from the diagnosis of dermatomyositis.^{58, 59} In a meta-analysis, the relative risk for developing malignancies was 4.4 for patients with dermatomyositis and 2.1 for patients with polymyositis.⁵⁸ The most common cancers occurring among patients with idiopathic inflammatory myopathies are breast and gynaecological cancers among women, lung cancer among men, and gastrointestinal malignancies among both sexes.

The temporal relation between cancer and idiopathic inflammatory myopathies is not clear. In a few cases of myositis a paraneoplastic mechanism was proposed. This was based on the observation of complete remission of myositis after resection of a malignant tumour without the use of corticosteroids.

Patients with malignant diseases, in particular those with haematological malignancies, may present with various forms of cutaneous vasculitic syndromes, vasculitis limited to a single internal organ, or a systemic form of vasculitis. Eight cases of vasculitis were diagnosed among 1730 cases of haematological malignancies.⁶⁰ Of 11 cases of cancer associated vasculitis, seven had a haematological neoplasm and four had a solid tumour.⁶¹ Reviews of published cases of cancer associated vasculitis showed that hairy cell leukaemia and lung cancer are the most common malignancies associated with vasculitis.⁶² Of 36 cases of solid tumour associated vasculitis, nine patients had lung cancer (seven cases of non-small cell cancer and two cases of small cell cancer).⁶³

Leucocytoclastic vasculitis is the most common type of vasculitis associated with malignancies. Of 14 cases of cancer associated vasculitis, seven (50%) were leucocytoclastic vasculitis. Small vessel vasculitis affecting the blood vessels of the peripheral nerves and muscles is also a common type of vasculitis seen in patients with malignancies. Vasculitis resembling polyarteritis nodosa has been associated mainly with hairy cell leukaemia.⁶⁴

As with dermatomyositis, there have been reports of patients presenting simultaneously with vasculitis and cancer. Of 29 patients with Wegener's granulomatosis, 14 presented simultaneously with cancer and vasculitis.⁶⁵ Other reported cases include the simultaneous diagnosis of vasculitis and lung cancer and the presence of small vessel vasculitis adjacent to stomach cancer in a histological examination of a resected stomach.⁶⁶ All those observations suggest a paraneoplastic mechanism for the occurrence of vasculitis among patients with cancers.

A 2.1-fold increased risk for the development of malignancies was seen among patients with SSc. The most common scleroderma associated cancers were breast and lung cancers. The relative risk for the development of lung cancer was 8.3, and all patients with scleroderma who developed lung cancer had pulmonary fibrosis before the diagnosis of cancer. Breast cancer was diagnosed concurrently with scleroderma. Most cases of breast cancer were diagnosed shortly after or before the diagnosis of scleroderma (within two years). Although a paraneoplastic mechanism for the development of scleroderma has not been reported, this temporal relation between the diagnosis of breast cancer and SSc may suggest a common genetic background, a possible shared cause, or a paraneoplastic syndrome.³

A paraneoplastic scleroderma syndrome has been reported among patients with POEMS syndrome. This syndrome occurs among patients with IgA plasmacytoma and is characterised by polyneuropathy, osteolytic lesions, hepatosplenomegaly, lymphadenopathy, and scleroderma-like features.

Hypertrophic osteoarthropathy is highly associated with non-SCLC. It is characterised by clubbing and painful swelling and tenderness of the distal phalanges. Histological examination discloses subperiosteal oedema and new bone formation along the shafts of the tubular bones of the limbs. Improvement in the hypertrophic pulmonary osteoarthropathy has been noted after chemotherapy or radiotherapy.^{67 68}

Sweet's syndrome is a clinical entity manifested by fever, neutrophilia, and tender erythematous coetaneous plaques of the arms, neck, and head. Musculoskeletal, pulmonary, and hepatic involvement may occur in this syndrome. Malignant diseases, most commonly acute myelogenous leukaemia, have been associated with this syndrome.⁶⁹

Autoimmune haematological paraneoplastic syndromes include autoimmune haemolytic anaemia and thrombocytopenia. These syndromes usually develop among patients with

chronic lymphocytic leukaemia and B cell lymphoma as a result of secretion of both warm and cold anti-red blood cells and anti-platelet autoantibodies.^{70 71}

Polycythaemia, as a result of erythropoietin secretion, has been associated with renal cell carcinoma, sarcomas, and pheochromocytomas.⁷²

Paraneoplastic syndromes of the nervous system are not common and occur in 1% of patients with malignant diseases.⁶⁵ Those syndromes are the result of activation of autoimmune mechanisms. Gene expression of onconeural antigens may result in the generation of anti-onconeural autoantibodies, leading to various neurological syndromes.^{29 73}

Encephalomyelitis is an inflammatory disease of the nervous system. It has been reported among patients with SCLC and anti-Hu antibodies. The inflammatory process may affect the dorsal ganglia, spinal cord, autonomic and peripheral nervous system.^{38 74 75}

Of patients with SCLC, 1–3% present with the Lambert-Eaton myasthenic syndrome (LEMS). Proximal muscle weakness, autonomic dysfunction, and involvement of the cranial nerves characterise this disorder.⁷⁶ Anti-voltage gated calcium channel antibodies have been found in the sera of patients with LEMS. They bind the active zone of the presynaptic cholinergic synapses and block the entry of calcium necessary for the release of acetylcholine.⁷⁷

Motor, sensory, or autonomic peripheral neuropathy may develop in patients with cancer. Patients with SCLC who generate high titres of anti-Hu antibodies develop an acute form and rapidly progressive sensory neuropathy of all limbs. Alternatively, they may present with autonomic polyneuropathy manifested by gastroparesis, postural hypotension, or urinary retention.⁷⁵ The motor peripheral neuropathies associated with the anti-Hu syndrome include Guillain-Barré syndrome among patients with Hodgkin's disease and anterior horn cell neuropathy among patients with lymphoma.

A peripheral polyneuropathy is found in about 5% of patients with Waldenström's macroglobulinaemia. In most of these cases the monoclonal component bind a glycuronyl sulphate epitope on a myelin associated glycoprotein (MAG). The binding of anti-MAG to peripheral nerves results in the development of demyelinating peripheral neuropathy.⁷⁸ Patients with multiple myeloma may develop peripheral sensorimotor polyneuropathy as a result of binding of IgG or IgA monoclonal proteins to 58, 43, and 8 kDa human endoneurium antigens.

Stiff man syndrome is characterised by severe spasm of the skeletal muscles. It has been reported among patients with SCLC, breast cancer, and thymoma and was found to be associated with anti-amphiphysin antibodies. This autoantibody reacts with a 128 kDa protein on the synaptic terminal that binds the vesicle core protein adaptor AP2 and dynamin. The binding of this autoantibody to amphiphysin prevents the release of neurotransmitters.⁷⁹ Neuromyotonia is another clinical entity

characterised by stiffness and prolonged activity of muscles. It has been associated with the anti-Hu antibody.⁷⁵

Various paraneoplastic syndromes of the kidneys have been reported. Membranous nephropathy, a clinical entity manifested by nephrotic syndrome, is highly associated with malignancies. Twenty two per cent of cases of idiopathic membranous nephropathy were found to have cancer, most commonly lung, colon, and stomach cancer. A deposition of cancer associated antigens has been found in the basement membrane of some of the patients with cancer associated membranous nephropathy.

Patients with lymphoproliferative malignancies, and in particular Hodgkin's lymphoma, also develop nephrotic syndrome, but the histological features are those of minimal change disease. It has been reported that up to 50% of patients with Hodgkin's lymphoma may develop minimal change glomerulopathy. Other renal paraneoplastic syndromes include the development of rapidly progressive glomerulonephritis among patients with plasma cell disorders and focal and segmental glomerulonephritis among patients with T cell lymphoma.⁸⁰

The data suggest that malignant transformation may be associated with immune dysregulation, activation of B and T cells, and the generation of a wide range of pathogenic autoantibodies that result in the development of various clinical entities.

POST-CHEMOTHERAPY RHEUMATISM

Patients with malignant diseases may develop rheumatic manifestations after chemotherapy. The first report of this association between chemotherapy and rheumatism was described among eight patients with breast cancer who were treated with adjuvant chemotherapy. All patients received cyclophosphamide combined with either methotrexate and fluorouracil or doxorubicin and fluorouracil. Rheumatic symptoms occurred 2–16 months after completing the chemotherapy and included myalgia, arthralgia, arthritis, periarticular swelling, and tenosynovitis. For all patients the erythrocyte sedimentation rate was normal and rheumatoid factor was not detected in their sera.⁸¹

Subsequent studies have reported a similar association between chemotherapy for breast cancer and rheumatism.^{82–83} This syndrome was also noted among patients with ovarian cancer and non-Hodgkin's lymphoma.^{83–84} In a review of 23 cases of women with breast cancer who developed rheumatism after chemotherapy, one patient developed SLE. However, that patient had autoimmune haemolytic anaemia before the diagnosis of breast cancer, suggesting that chemotherapy may activate autoimmune mechanisms.⁸⁵ It has also been noted that chemotherapy may worsen rheumatic symptoms among patients who had complaints before the chemotherapy.

The mechanism of this syndrome is not clear and may be multifactorial. Possible mechanisms include steroid withdrawal, early menopause, or side effects of cyclophosphamide and other chemotherapy agents.⁸⁶ Nine of the 23 patients included in Warner's series⁸⁵ developed their rheumatic symptoms shortly after beginning treatment with tamoxifen. In another study three patients developed inflammatory polyarthritis after treatment with tamoxifen.⁸⁷

Rheumatic and autoimmune features may develop after treatment with other chemotherapy agents. Raynaud's phenomenon may occur after treatment with bleomycin, vinblastine, and cisplatin.⁸⁸ Digital ischaemia and necrosis have been associated with 5-fluorouracil.⁸⁹ SSC-like disease has been reported after treatment with bleomycin. Raynaud's phenomenon, skin thickening, and pulmonary fibrosis characterise this entity.

Treatment of neoplastic diseases with immunomodulating agents may result in a state of autoimmunity. Interferon α treatment has been associated with the generation of autoantibodies and the induction of autoimmune disorders.⁹⁰ Thyroid autoantibodies, including antithyroglobulin and antithyroid peroxidase, and autoantibodies associated with autoimmune hepatitis, have been detected during and after treatment with interferon.⁹⁰ Similarly, symmetric polyarthritis, SLE, and other autoimmune diseases may develop after treatment with interferon.^{91–93}

Several cases of patients with myeloproliferative disorders including chronic myelogenous leukaemia and essential thrombocytosis developed SLE after treatment with interferon α and interferon γ .^{91–93} Twenty seven (20%) of 137 patients with chronic myelogenous leukaemia or essential thrombocytosis developed rheumatic symptoms⁹³ after interferon treatment. During interferon treatment 18 (72%) of 25 patients with chronic myelogenous leukaemia had antinuclear antibody positivity. Of these, 15 reported symptoms related to rheumatic diseases and three patients fulfilled the classification criteria for SLE. In another study 19% of 135 patients with malignant carcinoid syndrome developed autoimmune diseases, including autoimmune thyroid disease, SLE, pernicious anaemia, and vasculitis.⁹⁴

The data indicate that interferon treatment may trigger the development of autoimmunity and should not be used in patients with clinical and laboratory features suggesting autoimmune diseases.

Summary and conclusion

The data presented in this review suggest that autoimmune features and rheumatic manifestations occur in a relatively large proportion of patients with cancer.

This link between autoimmunity and cancer may result from a common aetiological origin (genetic, hormonal, or environmental factors) or, alternatively, from paraneoplastic syndromes.

A large number of autoantibodies have been identified, but little is known about their clinical significance. Although some of the autoantibodies are highly specific for cancer (anti-P53 and others), they present in less than 50% of the sera of patients with cancer. Therefore, they cannot be used for population screening for the early detection of cancer. Further studies are required to assess the diagnostic and/or prognostic value of autoantibodies reacting with oncoproteins, tumour suppression genes, and/or proliferation associated antigens

The close relation between neurological paraneoplastic syndromes and antineural autoantibody has a therapeutic implication, such as the use of gammaglobulins and specific anti-idiotypic treatment to suppress the levels of the pathogenic antibodies.

Finally, it is important to recognise that combination chemotherapy for malignant diseases may be associated with rheumatic manifestations that range from arthralgia and myalgia to an overt autoimmune rheumatic disease.

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