[Frontiers in Bioscience E2, 122-126, January 1, 2010]

A review of autoimmune diseases associated with cancer

Patricia Tai[1], Edward Yu[2], Kurian Joseph[3], Thomas Miale[4]

[1]Faculty of Oncology, University of Saskatchewan, Saskatchewan; [2]Department of Radiation Oncology, University of Western Ontario, London; [3]Department of Radiation Oncology, University of Edmonton, Alberta; [4]Department of Pediatric Oncology, Allan Blair Cancer Clinic, Saskatchewan, Canada

TABLE OF CONTENTS

1. ABSTRACT

The focus of this review is on the relationships between autoimmune diseases and cancer from two closely related perspectives: 1.Those autoimmune diseases which are often associated with malignancies. 2.Those prevalent cancers which may increase the risks of developing autoimmune disorders. The review concludes with a brief discussion of some selected innovative approaches to cancer immunotherapy.

2. INTRODUCTION

Recently emerging evidence has implicated infections and dietary proteins in the pathogenesis of both autoimmune diseases and cancer (1). Although this review correlates the common features with more recent investigational findings, the practical clinical relevance of some observations remains to be established. For example, autoimmune thyroid disease is associated with multiple myeloma [odds ratio=5.68, 95% confidence interval:1.69-

19.13] (2). Another illustrative example is autoimmune disease occurring in a long-term survivor of metastatic colon carcinoma treated with "GOLFIG-1," a newly developed translational anticancer regimen combining gemcitabine, oxalipatin, levofolinic acid and infusional 5-fluorouracil with the subcutaneous administration of two different immunoadjuvant cytokines: very low dose interleukin-2 (IL-2) and granulocyte-macrophage colony stimulating factor (GM-CSF, Leukine). The index patient reported responded favorably to this GOLFIG-1 regimen but unfortunately thereafter developed discoid lupus erythematosus.

Primary immunodeficiencies are genetic disorders that predispose to frequent and severe infections, autoimmunity and cancer (4). The expanded life span of patients with such deficiencies increases their overall period at risk for developing cancer, which is estimated presently at 4-25% (4). The type of malignancy correlates with the type of primary immunodeficiency, patient age and possibly antecedent viral infections. Non-Hodgkin lymphomas predominate, accounting for 60% of cases. The many heritable primary immunodeficiencies known to be associated with increased incidence of malignancy include: common variable immunodeficiency, IgA deficiency, severe combined immunodeficiency, Wiskott Aldrich syndrome, Klinefelter's syndrome, Chediak-Higashi syndrome, and ataxia telangiectasia syndrome. Acquired immunodeficiency states include hypogammaglobulinemia, iatrogenic immunosuppression, as induced during organ transplantations or thymic irradiation; or contracted with infections by the human immunodeficiency retrovirus (HIV). Human T-lymphotropic virus is associated with adult T cell leukemia-lymphoma. HIV causes acquired immune deficiency syndrome (AIDS) and the resulting immune deficiency states are associated with high-grade B cell lymphomas.

Many mediators and receptors may be involved in the development of malignancy. IL-21 is a type I cytokine produced by activated CD4+ T cells, natural killer T cells, and pro-inflammatory Th17 cells (5). IL-21 has many functions including: regulation of immunoglobulin production, promotion of Th17 differentiation, B cell terminal differentiation into plasma cells, cooperative expansion of CD8+ T cells, inhibition of antigen presentation by dendritic cells, and probable facilitation of both B-cell and natural killer cell apoptosis. Moreover, IL-21 has potent anti-tumor effects while it is also implicated in the development of autoimmune diseases. In addition, ongoing IL-21 research may improve treatments of many malignancies and autoimmune conditions.

However, cancer treatment of patients with immunodeficiencies is hampered by susceptibility to infections resulting from cytopenias and related complications of radiotherapy or chemotherapy. For example, immunocompetent patients might be able to effectively combat infections from widespread severe epithelial breaches as typically encountered in severe mucositis, but similar barrier compromises in immunodeficient patients often lead to life threatening septicemia. This imposes significant limitations on treatment intensity and may explain the generally poor treatment results for such unfortunate immunodeficient patients.

3. AUTOIMMUNE DISEASES ASSOCIATED WITH INCREASED CANCER RISK

Examples of autoimmune disorders associated with development of lymphomas are RA, SLE, SS, celiac disease and Hashimoto's thyroidits.

Although numerous case reports have been published describing an increased risk of acute and late toxicities in patients with collagen vascular diseases treated with radiotherapy, the results of large retrospective series are controversial. None of the three matched-controlled studies published to date has shown statistically significant increases in acute toxicities in this patient population (6-8). In fact, only one of these matched-controlled studies demonstrated a statistically significant increase in the risk of late complications in patients with collagen vascular diseases (6). This statistical significance disappeared with subset analysis by disease except for scleroderma. In contrast, the largest published retrospective series by Morris and Powell reported that non-RA patients, including patients with scleroderma and SLE, were at a significantly increased risk of developing late toxicities (8). A recent report suggested that radiotherapy might have been inappropriately withheld from patients with SLE (9). However, most radiation oncologists still consider active SLE a definite contraindication to treatment.

The following practical steps are suggested (10):

- A comprehensive pre-treatment conference should be organized by radiation oncologists for their patients to explain proposed therapy in great detail, toward a balanced discussion of both the potential benefits and the possible attendant increased risks of major acute and late toxicities of radiotherapy and/or other alternative treatments (10).
- Early and direct involvement of a rheumatologist to actively manage the patient's autoimmune disease before and during treatment might be useful especially to relieve the symptoms and lessen the impact of the complications.
- Initiation of nonsteroidal anti-inflammatory drugs or other therapies before the initiation of radiotherapy might lower the risk of immediate and late effects (8).
- The effect of concurrent chemotherapy on the development of complications has not been well established. However, concomitant use of chemotherapy should be avoided until more definitive data become available in most instances. Generally the concurrent chemotherapeutic effect is similar to adding an extra 8-10Gy to the total radiation (10).
    - Techniques to reduce the volume treated, total dose, and daily dose fractionation scheme have been suggested to minimize these risks (10).
    - All patients should continue to be monitored life-long to detect and mitigate severe late toxicities (10).

3.1. Rheumatoid arthritis (RA)

The risk of lymphomas is significantly increased in RA, whether treated with methotrexate, or other potent immunosuppressive agents, or not. Large granular lymphocyte proliferation may occur in some patients and even progress to T cell large granular lymphocytic leukemia.

3.2. Systemic lupus erythematosus (SLE)

The risk of non-Hodgkin lymphomas appears to be increased four to five fold. In particular, angioimmunoblastic T cell lymphoma may occur more often than expected.

3.3. Sjögren's Syndrome (SS)

Keratoconjunctivitis sicca refers to the ocular dryness associated with SS. Both SS and keratoconjunctivitis sicca are caused by immune-mediated inflammation directed against the exocrine glands of the eye and mouth. SS is characterized by polyclonal B cell activation as well as lymphocytic infiltration of the exocrine glands. This B cell activation predisposes some patients to the development of lymphomas. Most lymphomas arise from reactive pre-malignant infiltrates termed, "lymphoepithelial sialadenitis." The lifetime risk of non-Hodgkin lymphoma is increased 16 to 44 times the expected rate, to approximately five percent.

A variety of clinical features characterize patients with SS at increased risk for lymphoma: cutaneous vasculitis, peripheral neuropathy, rheumatoid factor positivity, type II cryoglobulins, antinuclear antibodies (anti-Ro/SSA or anti-La/SSB) positivity and infiltration of salivary glandular tissue by dendritic cells and macrophages expressing the cytokine receptors for IL-12 and IL-18.

3.4. Celiac disease (Non-tropical sprue)

Serological studies, now used to confirm the diagnosis of celiac disease, include the Enzyme-Linked ImmunoSorbent Assay (ELISA) for IgA antibodies to gliadin and the immunofluorescence test for IgA antibodies to endomysium, a structure in the smooth muscle connective tissue of the gut. Elevated serum levels of endomysial IgA antibodies are nearly pathognomonic. The target autoantigen contained within the endomysium was identified as tissue transglutaminase. IgA-antibodies against endomysium and the endomysial autoantigen tissue transglutaminase are both highly sensitive and specific. Widespread use of these serological tests has allowed earlier diagnosis, large scale population screening and thereby an improved recognition of this disorder. Implicit is that such testing is invalid in the many patients with an inherent but clinically silent IgA deficit. Particularly noteworthy is that patients with celiac disease have an increased incidence of gastrointestinal non-Hodgkin lymphomas.

4. AUTOIMMUNE PHENOMENON WITH CANCERS – PARANEOPLASTIC SYNDROMES

Paraneoplastic syndromes occur in increased frequency in patients with cancer and are not directly related to a primary or metastatic effect of their tumors, infections, metabolic abnormalities, or toxicities of their therapy (11,12). Autoantibodies and evidence for cellular autoimmunity directed against neuronal, glial, or muscle cell antigens have been identified in a number of paraneoplastic neurological disorders (13,14). Over the past four decades, different investigators identified and reported these disorders often coining a variety of new specific descriptive terms. This review employs the widely accepted nosology proposed by Posner (14). Although paraneoplastic disorders are rare, accurate diagnosis remains important. In addition, for patients with occult malignancies, the correct diagnosis of these paraneoplastic disorders may lead also to the early diagnosis and treatment of underlying malignancies. Effective treatment of the neurological disorder may reduce neurological dysfunctions and improve overall quality of life. Equally important, proper diagnosis of a paraneoplastic disorder spares the patient an extensive and expensive search for alternative more benign underlying causes of the neurological dysfunction.

4.1. Neurological

Examples of neurological paraneoplastic syndromes include: subacute sensory neuronopathy and encephalomyeloneuritis, limbic encephalitis, autonomic neuropathy, progressive cerebellar degeneration, vision loss, opsoclonus-myoclonus, motor neuron disorders, peripheral neuropathies, neuromuscular junction disorders, muscle rigidity, dermatomyositis, polymyositis and movement disorders. More extensive descriptions of each of these various paraneoplastic conditions are included in the current edition of a leading textbook (15). The most commonly encountered neurological paraneoplastic syndromes often encountered in the clinical practice of oncology are discussed in the next section.

4.1.1. Neuromuscular Junction Disorders

4.1.1.1. Lambert-Eaton myasthenic syndrome (LEMS)

LEMS is associated with 50-60% of small cell carcinoma of the lung (15). Characteristic electrophysiological abnormalities include augmentation of compound motor action potentials with repetitive stimulation. Antibodies directed against protein epitopes in voltage-gated calcium channels of presynaptic neurons are present in most patients with LEMS. Passive transfer of antibodies reproduces characteristic electrophysiological abnormalities in animal models of LEMS. Unlike those with other paraneoplastic syndromes, most patients with LEMS benefit from plasmapheresis and immunosuppressive therapy. Drugs increasing presynaptic acetylcholine release may also decrease symptoms. 3,4-diaminopyridine is one such agent with relatively minimal deleterious side effects. Patients with LEMS have an improved prognosis compared with their counterparts with the same tumors at similar stages but lacking such associated neurological deficits (16).

4.1.1.2. Myasthenia Gravis (MG)

MG is associated with thymoma in approximately 15% of cases (15). Autoantibodies against contractile proteins of striated muscle are found. All such MG patients should undergo thoracic imaging studies

promptly to identify thymic neoplasms. In patients with thymoma, MG often remits after thymectomy. In almost all cases, the thymoma is not invasive and can be definitively treated by thymectomy only. One unfortunate patient referred to us with unrecognized and untreated MG ultimately died from resulting respiratory failure shortly after referral.

4.1.2. Dermatomyositis and polymyositis

These conditions are inflammatory myopathies characterized by the subacute development of proximal muscle weakness, with or without pain and muscle tenderness. Both conditions are usually idiopathic. Approximately 10% are associated with cancer (15). The myopathy usually precedes the diagnosis of the underlying cancer. Although most patients with dermatomyositis do not have a concurrent malignancy, they are probably at a higher risk for cancer. In particular, when the characteristic findings are present in men older than 40 years, there is a much higher incidence of underlying cancer. Early detection should be a priority in such men. Breast cancer is the most commonly associated cancer in women; and lung and gastrointestinal cancer, in men. Association with tumors of the pancreas, melanoma, germ cell tumors, nasopharyngeal carcinoma, and lymphoma also has been reported.

An immune-mediated intramuscular angiopathy leads to eventual ischemia and muscle fiber necrosis. IgG, IgM, and complement deposits are found in small blood vessels. Cellular inflammatory infiltrates include CD4+ T cells, B cells, and macrophages. Immunosuppression has not been tested specifically in patients with myositis. It is unclear if antineoplastic therapy leads to improvement in the muscle disease. Both dermatomyositis and polymyositis syndromes follow an inconsistent course, often independent of the cancer outcome.

4.2. Hematological

Autoimmune hemolytic anemias are typically associated with B cell malignancies, including chronic lymphocytic leukemia and lymphoma. These anemias arise secondary to immunoregulatory abnormalities in these diseases, rather than to a direct secretion of tumor-derived substances (15). Hallmarks of this disorder are a positive direct antiglobulin (Coombs') tests, elevated reticulocyte counts, decreased haptoglobin levels, and elevated lactate dehydrogenase levels. Warm or cold antibody autoimmune hemolytic anemias are particularly prevalent with small lymphocytic lymphomas. Additional autoimmune phenomena, such as circulating anticoagulants (e.g., acquired von Willebrand's disease) may occur, especially in these small lymphocytic lymphomas.

Warm antibody hemolytic anemia is most commonly associated with lymphoma, chronic lymphocytic leukemia, and mucin-producing adenocarcinoma. Cold agglutinin disease is most common in Waldenström's macroglobulinemia and lymphomas (17). Autoimmune hemolytic anemia is rarely associated with solid tumors. However, an association with ovarian, gastrointestinal, lung, breast, and renal cell cancers has been reported occasionally (17). Corticosteroid treatment appears to be less effective in autoimmune hemolytic anemias associated with carcinomas than the more common idiopathic variants or those associated with lymphoid malignancies.

5. NEW PERSPECTIVES ON CANCER VACCINES

Immunotherapy for melanoma has undergone significant refinements since the pioneering attempts to treat patients with high dose IL-2. There are now strategies to boost patient antitumor immunity through vaccinations, treatment with agents that augment host immunity, and adoptive cell transfer (18). Unfortunately, however, the first two strategies have yielded only limited clinical success.

Over the last century, vaccine studies have demonstrated that human immune systems, with appropriate augmentation, can limit or prevent infections by otherwise lethal pathogens (19). Encouraged by these antimicrobial results, success in animal models and numerous well-documented reports of immune-mediated melanoma regression in humans, investigators developed melanoma vaccines. However, despite considerable laboratory evidence for experimental vaccine-induced immune responses in various research settings, reliably positive clinical responses remain generally elusive. Recent studies have elucidated several mechanisms which may hinder or prevent the development of successful vaccines and suggest novel approaches to overcome these barriers. Unraveling the mechanisms of autoimmunity, dendritic cell activation, regulatory T cells and Toll-like receptors will generate novel vaccines that may result in improved clinical outcomes, when used in conjunction with standard adjuvant therapies.

Adoptive cell transfer therapy, particularly following strenuous lymphocyte depleting, preconditioning regimens, has resulted in objective response rates approaching 50% (18). Balancing antitumor efficacy, autoimmunity, and reconstitution of a functioning immune system remain challenging and often involve serious, and even potentially life-threatening issues. Nonmutated tissue differentiation antigens expressed by tumors are attractive targets for cancer immunotherapy, but the harm of such highly effective antitumor treatments to normal tissues has not been fully characterized. The infusion of *ex vivo* expanded adoptively transferred melanoma/melanocyte-specific CD8+ T cells that mediated robust tumor killing also induced autoimmune destruction of melanocytes in the eye (20). This severe autoimmunity was associated with the intraocular up-regulation of MHC class I molecules and high levels of IFN-gamma derived from both adoptively transferred CD8+ T cells and host cells. Furthermore, ocular autoimmunity required the presence of the IFN-gamma receptors on target tissues. Data compiled from more than 200 eyes and their associated tumors in 10 independently performed experiments revealed a highly significant correlation between the efficacy of tumor immunotherapy and the severity of ocular autoimmunity ($P<0.0001$). Fortunately administration of high doses of steroids locally mitigated ocular autoimmunity without impairing the antitumor effect. These findings have

particular importance for immunotherapies directed against self-antigens and highlight the need for targeting unique tumor antigens not normally present in ocular tissues.

6. REFERENCES

1. A. Vojdani: Antibodies as predictors of complex autoimmune diseases. *Int J Immunopathol Pharmacol* 21, 267-278 (2008)

2. M. Dalamaga, K. Karmaniolas, E. Papadavid, N. Pelecanos and I. Migdalis: Association of thyroid disease and thyroid autoimmunity with multiple myeloma risk: a case-control study. *Leuk Lymphoma* 49, 1545-1552 (2008)

3. P. Correale, A. Fioravanti, I. Bertoldi, F. Montagnani, C. Miracco and G. Francini: Occurrence of autoimmunity in a long-term survivor with metastatic colon carcinoma treated with a new chemo-immunotherapy regimen. *J Chemother* 20, 278-281 (2008)

4. K. Salavoura, A. Kolialexi, G. Tsangaris and A. Mavrou: Development of cancer in patients with primary immunodeficiencies. *Anticancer Res* 28(2B), 1263-1269 (2008)

5. R. Spolski and WJ. Leonard: The Yin and Yang of interleukin-21 in allergy, autoimmunity and cancer. *Curr Opin Immunol 20*, 295-301 (2008)

6. A.M. Chen and E. Obedian, B. Haffty: Breast-conserving therapy in the setting of collagen vascular disease. *Cancer J* 7, 480–491 (2001)

7. C. Phan, M. Mindrum, C. Silverman, K. Paris and W. Spanos: Matched-control retrospective study of the acute and late complications in patients with collagen vascular diseases treated with radiation therapy. *Cancer J* 9, 461–466 (2003)

8. M.M. Morris and S.N. Powell: Irradiation in the setting of collagen vascular disease: Acute and late complications. *J Clin Oncol* 15, 2728–2735 (1997)

9. V. Benk, A. Al-Herz, D. Gladman, M. Urowitz and P.R. Fortin: Role of radiation therapy in patients with a diagnosis of both systemic lupus erythematosus and cancer. *Arthritis Rheum* 53, 67–72 (2005)

10. J.Wo and A. Taghian: Radiotherapy in setting of collagen vascular disease. *Int J Radiat Oncol Biol Phys* 69, 1347–1353 (2007)

11. P.D. Clouston, L.M. De Angelis and J.B. Posner: The spectrum of neurologic disease in patients with systemic cancer. *Ann Neurol* 31, 268 (1992)

12. Paraneoplastic syndromes. In: Neurologic complications of cancer. Ed: Posner JB. Philadelphia: *FA Davis*, (1995)

13. J. Dalmau and J.B. Posner: Neurologic paraneoplastic antibodies (anti-Yo, anti-Hu, anti-Ri): the case for a nomenclature based on antibody and antigen specificity. *Neurology* 44, 2241 (1994)

14. J.B. Posner and H.M. Furneaux: Paraneoplastic syndromes. In: Immunologic mechanisms in neurologic and psychiatric disease. Ed: Waksman BH. New York: *Raven Press*, (1990)

15. M. Boyiadzis, F.S. Lieberman, L.J. Geskin and K.A. Foon. In: Cancer Principles and practice of Oncology. Eds: V.T. DeVita Jr., T.S. Lawrence, S.A. Rosenberg. Philadelphia: *Lippincott Williams & Wilkins* (2008)

16. P. Maddison and B. Lang: Paraneoplastic neurological autoimmunity and survival in small-cell lung cancer. *J Neuroimmunol* 201-202, 159-162 (2008)

17. L.P. Akard, J. Brandt, L. Lee, J. Jansen and R. Hoffman: Chronic T cell lymphoproliferative disorder and pure red cell aplasia. *Am J Med* 83, 1069 (1987)

18. L. Fang, A.S. Lonsdorf and S.T. Hwang: Immunotherapy for advanced melanoma. *J Invest Dermatol* 128, 2596-2605 (2008)

19. L.B. Riley and S.S. Agarwala: Melanoma vaccines. *Expert Rev Vaccines* 7, 937-949 (2008)

20. D.C. Palmer, C.C. Chan, L. Gattinoni, C. Wrzesinski, C.M. Paulos, C.S. Hinrichs, D.J. Powell Jr, C.A. Klebanoff, S.E. Finkelstein, R.N. Fariss, Z. Yu, R.B. Nussenblatt, S.A. Rosenberg and N.P. Restifo: Effective tumor treatment targeting a melanoma/melanocyte-associated antigen triggers severe ocular autoimmunity. *Proc Natl Acad Sci U S A* 105, 8061-8066 (2008)

Abbreviations: AIDS: acquired immune deficiency syndrome, ELISA: Enzyme-Linked ImmunoSorbent Assay, GOLFIG-1: gemcitabine, oxalipatin, levofolinic acid and infusional 5-fluorouracil, interleukin-2 and granulocyte-macrophage colony stimulating factor, GM-CSF: recombinant granulocyte-macrophage colony stimulating factor, Gy: Gray or energy absorbed per unit mass: unit is joule per kilogram, HIV: human immunodeficiency virus, IL: interleukin, LEMS: Lambert-Eaton myasthenic syndrome, RA: rheumatoid arthritis, SLE: systemic lupus erythematosus, SS: Sjögren's syndrome, Th17: proinflammatory T cells, anti-Ro/SSA, anti-La/SSB, B cells, CD, IFN, IgA, IgG, IgM, MHC, T cells

Key Words: Autoantibody, Autoimmunity, AIDS, Cytokine, Cancer, Review

Send correspondence to: Patricia Tai, Allan Blair Cancer Clinic, 4101 Dewdney Ave, Regina, Saskatchewan, Canada S4T 7T1 Tel: 306-766-2296, Fax: 306-766-2777, E-mail: ptai2@yahoo.com

http://www.bioscience.org/current/vol2E.htm