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ANCA-associated vasculitis and malignancy: Current evidence for cause and consequence relationships

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In this review, we summarise the current understanding of the potential link between cancer and anti-neutrophil cytoplasmic antibody-associated vasculitis (AAV), including granulomatosis with polyangiitis (Wegener's; GPA) and microscopic polyangiitis (MPA). As is true for many autoimmune or inflammatory rheumatic diseases, AAV diagnosis and therapy are associated with an increased risk of *de novo* cancer development, likely as a result of impaired immunosurveillance, direct oncogenicity of immunosuppressive agents and perhaps malignant degeneration of tissues undergoing chronic immune stimulation. Data from several studies suggest a standardised incidence ratio of cancer in AAV of 1.6–2.0 compared to the general population and a possibly higher risk in GPA than in MPA. The most prominent cancers observed in AAV include urinary tract cancer, leukaemia and non-melanoma skin cancer. The effect of individual therapeutic agents is difficult to dissect, but cyclophosphamide has emerged as a major contributor to cancer development because of its direct carcinogenic properties. Awareness of cancer risk in AAV calls for increased implementation of measures to prevent or screen for cancer and development of less carcinogenic therapies. Cancer has also been suggested as a potential trigger or cause of AAV. Although some

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studies found that prior or concomitant history of cancer increases the risk of AAV, available data are inconsistent and suggest that the fraction of AAV that might be attributable to cancer is at best small.

Introduction

Anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAV), which includes the subentities granulomatosis with polyangiitis (Wegener's; GPA) and microscopic polyangiitis (MPA), is an organ- and life-threatening chronic inflammatory small-vessel vasculitis. It predominantly affects adults, without gender preference. GPA and MPA are commonly grouped together because of their clinical–pathological commonalities and their tight association with positive ANCA serology. However, unlike MPA, GPA has features of granulomatosis with unique head and neck as well as lung manifestations and a more chronically relapsing disease course [1,2].

AAV therapy is based on glucocorticoids combined with an immunosuppressive agent. Tailoring therapy to disease severity and more effective therapeutic regimens have led to increased survival, but relapse risk remains high and some patients are maintained on prolonged immunosuppressive therapy. An important conceptual step forward was the splitting of AAV therapy into remission-induction and -maintenance phases, which aimed to reduce therapy-related toxicity by limiting the use of cyclophosphamide, a pivotal drug used in AAV. Another major shift in AAV therapy has been the recent evidence of the benefits of targeted biologic treatment with rituximab as a substitute for conventional immunosuppressive drugs [1,3].

As AAV therapy became more successful, research has increasingly focused on survivor prognosis in the long term. The concern is that the short-term efficacy of therapy might be compromised by untoward long-term outcomes such as cardiovascular and cancer morbidity [1]. Cancer development is a significant problem because of the impact on survival and quality of life. Adequate identification of this association is important for prevention and screening measures.

Cancer has also been linked with AAV as a potential causal or disease-triggering factor. The aetiology of AAV is not well understood and likely involves multiple genetic and non-genetic determinants [4]. AAV is generally considered a primary vasculitis, but infectious agents, drugs or cancer could be aetiological factors. Understanding the link between cancer and AAV development is crucial for understanding AAV pathogenesis and for clinical practice.

This review summarises the current knowledge of the interaction between AAV and malignancy occurring during AAV or as a potential cause.

AAV and *de novo* cancer risk

Many chronic primary autoimmune and/or inflammatory diseases have been associated with increased risk of *de novo* cancer development. People diagnosed with rheumatoid arthritis [5–7], systemic lupus erythematosus [8,9], systemic sclerosis [10,11] or primary Sjögren's syndrome [12] have a statistically significant increased overall cancer risk, with reported standardised incidence ratios (SIRs) of 1.1–1.5.

Several pathways likely intervene in cancer development in chronic autoimmune and inflammatory diseases. Immunosuppressive therapy decreases the immune system's ability to recognise and eliminate malignant cell clones and may have direct mutagenic properties. These effects are highlighted by the strikingly increased risk of a broad range of cancers in patients with human immunodeficiency virus/acquired immunodeficiency syndrome (HIV/AIDS) and renal transplant recipients [13]. Long-standing immune activation *per se* may be oncogenic and is thought to explain the increased rate of lymphoma seen in a number of chronic autoimmune and inflammatory rheumatisms [14]. Such immune activation may explain the high risk of colorectal cancer in ulcerative colitis [15] and the increased risk of lung cancer in auto-immune and inflammatory diseases commonly manifesting with pulmonary