

# Contents

<b>Foreword</b>	<b>xi</b>
-----------------	-----------

Michael H. Weisman

<b>Preface: Timely Knowledge and Clinical Insights on Cancer and Rheumatic Disease</b>	<b>xiii</b>
--	-------------

John Manley Davis III

<b>Overview of the Associations Between Cancer and Rheumatic Disease</b>	<b>417</b>
--	------------

John Manley Davis III

People living with rheumatic diseases frequently encounter cancer, either as a potential harm of antirheumatic therapies or as a comorbidity that alters the conversation about management. This article provides a general overview of the issues related to cancer and rheumatic disease and serves as a springboard for the remaining chapters in this issue. Several topics are reviewed, including epidemiology, bidirectional causal pathways, and issues related to medications. Although uncertainties remain, the issue of cancer is of great importance to patients with rheumatic diseases, and an individualized, person-centered approach to assessment and management is necessary.

<b>Autoimmunity, Clonal Hematopoiesis, and Myeloid Neoplasms</b>	<b>429</b>
--	------------

Delamo I. Bekele and Mrinal M. Patnaik

Clonal hematopoiesis has been linked with the development of hematologic malignancy and atherosclerotic cardiovascular disease; however, the association with autoimmune diseases remains to be defined. The link between autoimmune diseases and myeloid neoplasms (MNs) is complex, often multifactorial, and seems bidirectional. The limited data suggest an increased risk of MNs in rheumatoid arthritis and systemic lupus erythematosus. Paraneoplastic manifestations of MN include arthritis, vasculitis, and connective tissue disease. Treatment options for autoimmune disease such as cyclophosphamide and azathioprine have been associated with MNs, whereas the data for methotrexate and tumor necrosis factor inhibitors are equivocal.

<b>Cancer and Rheumatoid Arthritis</b>	<b>445</b>
--	------------

Xerxes Pundole and Maria E. Suarez-Almazor

Management of rheumatoid arthritis (RA) in patients with cancer is complex and requires a multidisciplinary approach. A few studies have examined the risk for recurrence in patients with RA receiving disease-modifying antirheumatic drugs, primarily tumor necrosis factor- $\alpha$  inhibitors. Although these agents seem to be safe in patients with a history of cancer and no evidence of disease, additional information is needed to determine their potential effects in patients with RA and active cancer. Patients with RA undergoing cancer therapy, including surgery, radiation, chemotherapy,

and immunotherapy, need to be carefully monitored because they are at increased risk for adverse events.

**Risk of Malignancy in Spondyloarthritis: A Systematic Review** **463**

Paras Karmacharya, Ravi Shahukhal, and Alexis Ogdie

Systematic inflammatory diseases, including rheumatoid arthritis (RA), are associated with an increased risk of malignancies. However, the pathogenesis of spondyloarthritis (SpA), which includes both ankylosing spondylitis and psoriatic arthritis, is different from RA, and the risk of malignancy and sites involved may also be different. It is important to better understand associations of SpA with site-specific cancers to facilitate appropriate cancer screening. The goal of this review was to examine the association of SpA with malignancy and the potential impact of therapy for SpA on development of malignancy.

**Sjögren Syndrome and Cancer** **513**

Ann Igoe, Sali Merjanah, and R. Hal Scofield

The association between malignancy and rheumatic diseases has been demonstrated in a multitude of studies. Little is understood regarding the pathogenesis of rheumatic and musculoskeletal diseases in association with malignancy. There is strong evidence regarding the association between Sjögren syndrome and lymphoma as well as risk factors for development of lymphoma in these patients. This article discusses the accumulating data on various malignancies described in primary Sjögren syndrome, highlighting non-Hodgkin lymphoma and thyroid, multiple myeloma, and skin cancers. These reported associations may have clinical implications in daily practice and contribute to understanding of both autoimmunity and cancer.

**Cancer and Systemic Lupus Erythematosus** **533**

Alexandra Ladouceur, Basile Tessier-Cloutier, Ann E. Clarke, Rosalind Ramsey-Goldman, Caroline Gordon, James E. Hansen, and Sasha Bernatsky

Systemic lupus erythematosus is associated with a small overall increased cancer risk compared with the general population. This risk includes a 4-fold increased risk of non-Hodgkin lymphoma, but a decreased risk of other cancers (such as breast cancer). The pathophysiology underlying the increased risk of hematologic cancer is not fully understood, but many potential mechanisms have been proposed, including dysfunction of the tumor necrosis factor and other pathways. A decreased risk of breast, ovarian, and endometrial cancer might be driven by hormonal factors or lupus-related antibodies, but these links have not been proved.

**Cancer and Scleroderma** **551**

Emma Weeding, Livia Casciola-Rosen, and Ami A. Shah

Individuals with scleroderma have an increased risk of cancer compared with the general population. This heightened risk may be from chronic inflammation and tissue damage, malignant transformation provoked by immunosuppressive therapies, or a common inciting factor. In unique

subsets of patients with scleroderma, there is a close temporal relationship between the onset of cancer and scleroderma, suggesting cancer-induced autoimmunity. This article discusses the potential mechanistic links between cancer and scleroderma, the serologic and clinical risk factors associated with increased cancer risk in patients with scleroderma, and implications for cancer screening.

### **Risk Factors and Cancer Screening in Myositis**

565

Siamak Moghadam-Kia, Chester V. Oddis, Dana P. Ascherman, and Rohit Aggarwal

The idiopathic inflammatory myopathies, particularly dermatomyositis, are associated with an increased risk of cancer. Lung, ovarian, breast, colon, prostate, and cervical cancers, and hematologic malignancies, are among the most common associated cancers. Risk stratification for cancer in patients with myositis is based on clinical risk factors/red flags, myositis clinical subtypes, and myositis-specific autoantibodies. Clinical risk factors include older age at disease onset, male gender, dysphagia, acute onset/refractory myositis, cutaneous ulceration, necrosis/vasculitis, and elevated inflammatory markers. Appropriate screening strategies are based on the risk level. Further studies are warranted to determine the role of advanced imaging and comprehensive cancer screening.

### **Paraneoplastic Musculoskeletal Syndromes**

577

Fahad Khan, Hilary Kleppel, and Alexa Meara

Paraneoplastic syndromes are rare diseases caused by malignancies through means other than mass effect or metastasis. Paraneoplastic phenomena can be the first sign of cancer and can be fatal. Paraneoplastic rheumatic syndromes can occur with hematologic cancers, lymphoproliferative disease, and solid tumors. Diseases that feature an advanced age at onset, significant constitutional upset, inadequate response to treatment, and otherwise atypical characteristics should increase the index of suspicion for a paraneoplastic syndrome.

### **Immune Checkpoint Inhibition—Does It Cause Rheumatic Diseases? Mechanisms of Cancer-Associated Loss of Tolerance and Pathogenesis of Autoimmunity**

587

Uma Thanarajasingam and Noha Abdel-Wahab

Mechanisms of immune checkpoints and their role in autoimmunity are discussed in the context of immune checkpoint inhibitor (ICI) therapy for cancer. The updated clinical spectrum of immune-related adverse events (irAEs), with an in-depth discussion of rheumatic irAEs, is presented. The relationship between ICI-induced loss of self-tolerance in cancer and the implications for understanding of irAEs, rheumatic irAEs in particular, is overviewed.