Overview of the Associations Between Cancer and Rheumatic Disease

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KEYWORDS

• Cancer • Malignancy • Rheumatic disease • Prognosis
• Immune checkpoint inhibitors • Immune-related adverse events • Treatment
• Biologic therapies

KEY POINTS

- People with rheumatic diseases in general experience a higher risk of cancer compared with their peers in the general population; the types of cancer and the magnitude of risk differ across the rheumatic diseases.
- Chronic immune activation and inflammation caused by rheumatic diseases seem to be central to the increased risk of malignancies experienced by patients.
- Bidirectional relationships exist between cancer and rheumatic diseases; this is best exemplified by emerging data in myositis and systemic sclerosis.
- Rheumatic immune-related adverse effects of immune checkpoint inhibitors for the treatment of various cancers highlight a delicate balance between malignancy and inflammatory rheumatic syndromes and are an emerging clinical challenge for management.
- When facing patients with an underlying rheumatic disease, it is crucial to appraise the individuals' knowledge, preferences, and values and engage them in shared decision making about options for management.

INTRODUCTION

Cancer is a vexing issue that frequently confronts patients with rheumatic diseases and their physicians. Many different types of cancer have been associated with rheumatic diseases, including hematologic and nonhematologic malignancies. In contrast, many different rheumatic diseases have known associations with malignancy. These points inform a variety of considerations regarding potential causality. First, inflammation is central to both cancer and rheumatic disease, which may explain in part the overlap in risk factors. Second, there are many examples of rheumatic diseases being associated with heightened risk of cancer, and there are examples of cancers potentially causing rheumatic diseases such as paraneoplastic syndromes, showing the

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bidirectional relationships between these neoplastic and inflammatory disease states. Third, medications may mediate the relationship between cancer and rheumatic disease. Although concerns have arisen that immunosuppressive, disease-modifying antirheumatic therapies may increase the cancer risk, long-term extensions of clinical trials as well as population-based trials increasingly provide reassurance that these agents can be used overall with safety with regard to cancer risk. More recently, an epidemic of rheumatic immune-related adverse events of checkpoint inhibitor therapy is transforming understanding of the interactions between immunity and oncogenesis. In this issue of *Rheumatic Disease Clinics of North America*, experts review the complex interrelationships between cancer, rheumatic disease, and treatment of these conditions in depth. They address key points to consider regarding cancer screening for patients with rheumatic diseases. Ultimately, this issue is expected to provide state-of-the-art information to guide clinicians and their patients.

OVERVIEW OF THE ASSOCIATIONS BETWEEN CANCER AND RHEUMATIC DISEASE

For the past several decades, knowledge of the relationship between cancer and rheumatic disease has been in existence. Historically, this knowledge has been classified according to hematologic and nonhematologic (ie, solid or visceral) malignancies. With respect to the hematologic category, higher rates of both lymphoid (eg, Hodgkin and non-Hodgkin lymphoma) and myeloid (eg, acute myeloid leukemia) neoplasms have been reported among patients with several rheumatic diseases; for example, rheumatoid arthritis (RA),[1–3] systemic lupus erythematosus,[4–7] and Sjögren syndrome.[8–10] More recently, as reviewed in this issue by Bekele and Patnaik,[11] an emerging relationship between rheumatic disease and clonal hematopoiesis provides new insights into the relationships between chronic inflammation and malignant cell transformation.[12]

With regard to the nonhematologic category, differential risk has been observed for various types of solid/visceral malignancies among patients with rheumatic diseases, including melanoma and nonmelanoma skin cancers, and breast, lung, liver, pancreas, bladder, prostate, uterine, and cervical cancers.[1,4,13–16] Associations vary in terms of cancer types and even direction of effect across the rheumatic diseases, which presumably may be related to basic demographics, risk factors, levels and sites of systemic inflammation, or degree of immune suppression associated with the antirheumatic therapies used. In this issue, Igoe and colleagues[17] highlight not only the hematologic but also the nonhematologic malignancies that associate with Sjögren syndrome, including the salivary glands, nasopharynx, thymus, and lung. As highlighted by Pundole and Suarez-Almazor[18] in this issue, preexisting interstitial lung disease in patients with RA is a risk factor for the development of lung cancer, which may relate to smoking as a shared risk factor or to chronic inflammation and activation of fibrogenic pathways. In an example of different associations by cancer type, the risks of lung cancer and melanoma are increased for patients with RA but decreased for breast and colorectal cancer.[19] Recently, it has been shown that the reduced risk of breast cancer in patients with RA cannot be explained by traditional risk factors.[20] The incidence rates for high-grade cervical dysplasia and cancer are higher for patients with systemic lupus erythematosus (SLE) than for patients with rheumatoid arthritis or psoriasis.[16] Further research is necessary to elucidate the underpinnings of these differential associations between cancer and rheumatic diseases.

OVERVIEW OF SHARED RISK FACTORS

In reviewing the most important risk factors for both cancer and rheumatic disease, it is likely that many of these are shared between the two disease categories. Previous studies have attempted to address the extent to which genetic risk factors overlap

between cancer and rheumatic diseases. If genetic overlap plays an important role in the risk of these two conditions, the familial risk associations would be expected to be bidirectional. However, in the example of the association between RA and lymphoma, a personal history of cancer, including lymphoma, does not increase the risk of subsequent RA development. Similarly, having a family history of Sjögren syndrome does not associate with a higher risk of non-Hodgkin lymphoma, and vice versa.[21] A confirmed example of genetic overlap between cancer and rheumatic disease has been reported for Sjögren syndrome, in which genetic variation in tumor necrosis factor alpha–induced protein 3 (TNFAIP3), the gene that encodes the A20 protein and that is associated with several autoimmune diseases, has been found to be present in 77% of these patients who develop mucosa-associated lymphoid tissue lymphoma.[22] A recent large genome-wide association study has shown sparse overlap between genetic variants associated with RA, SLE, and non-Hodgkin lymphoma subtypes; however, only a few weakly associated loci were identified in common, explaining little overall risk.[23] Hence, it seems likely that other factors are more important in the risk of cancer in patients with rheumatic diseases.

One such factor that is central to both cancer and rheumatic disease is chronic inflammation, with numerous examples in the literature. In particular, this would partially explain why so many cancers follow the onset of autoimmune rheumatic diseases, such as in the cases of rheumatoid arthritis, lupus, and Sjögren syndrome.[24] For example, the incidence of lymphoma increases in the decade following the onset of RA.[24] The risk is highest among patients in the upper decile of cumulative disease activity and tends to decrease with use of disease-modifying medications to control disease activity.[25,26] In the case of Sjögren syndrome, the presence of rheumatoid factor and measures of disease activity (eg, low C4 level; cryoglobulinemia; lymphopenia; and the European League Against Rheumatism Sjögren's Syndrome Disease Activity Index, excluding the lymphoma domain) were found to be predictive of lymphoma.[27] The concept that chronic activation of the immune system, either by infection or autoimmune disease, mediates cancer development also holds for acute and chronic myeloid leukemias.[28,29] Using the Veterans Affairs Rheumatoid Arthritis cohort, Bryant and colleagues[30] showed that increased levels of cytokines and chemokines in the peripheral blood at baseline of men with RA was associated during longitudinal follow-up with overall cancer mortality. Furthermore, there was an interaction between tobacco smoking and the summary cytokine score, such that cancer mortality was much higher among men who were current smokers and had a high cytokine score than for either risk factor alone. With regard to gout, a disease that has been of great interest in recent years, there is increasing evidence that chronic gouty inflammation is associated with an increased risk of malignancies,[31–33] which may be attenuated by colchicine or urate level–lowering therapy.[34–36] In addition, aspirin and nonsteroidal antiinflammatory drugs in a recent meta-analysis were shown to decrease the risk of recurrent colorectal adenomas, a precursor to adenocarcinoma.[37] Hence, ongoing efforts to abrogate inflammation in patients with rheumatic diseases will be crucial to effectively mitigate risk of future malignancy.

Environmental risk factors are also shared between cancer and rheumatic diseases. Tobacco smoking is a well-known risk factor for both rheumatic diseases (eg, RA, SLE, and Sjögren) and a myriad of cancers, especially lung cancer.[38–42] Excess body fat and obesity are also established risk factors for several rheumatic diseases and cancers, the effects of which in these diseases may be mediated by the issue of chronic inflammation, mentioned earlier.[43–45] Dietary patterns, particularly those with inflammation-promoting foods, are associated with a higher risk of both RA and certain cancers.[46–52] The molecular mechanisms of these associations remain

to be defined, but there is great interest in the role of the gut microbiome in mediating the effects of inflammatory dietary patterns on the host immune system, ultimately driving adaptive immune responses and chronic inflammation.[53–57] There may also be a role for the gut microbiome in driving cell growth and proliferation, altering food and drug metabolism, and modulating immune surveillance for malignant cells via the effects of circulating microbial metabolites.[54] It is also possible that live gut bacteria translocate across a dysfunctional gut barrier to interact with and instigate T-cell and B-cell activation and inflammatory responses that could play a role in both cancer and rheumatic diseases.[53,55,56] In addition, Epstein-Barr virus is an example of a viral pathogen that has been associated with lymphoproliferative disease in patients treated with immunosuppressive therapies, both in the cancer and rheumatic setting, and is also associated with the pathogenesis of RA, SLE, and Sjögren syndrome.[58,59]

POTENTIAL CAUSAL PATHWAYS FROM CANCER TO RHEUMATIC DISEASE

It has been known for decades that rheumatic conditions can represent paraneoplastic syndromes. As reviewed comprehensively in this issue by Khan and colleagues,[60] classical paraneoplastic rheumatic syndromes include carcinomatous polyarthritis, remitting symmetric seronegative synovitis with pitting edema (RS3PE), polymyalgia rheumatica–like syndromes, and palmar fasciitis with polyarthritis.[61–64] Recently, the spectrum of autoimmune and autoinflammatory syndromes associated with chronic myelomonocytic leukemia has become apparent.[65] Great progress has been made in understanding the nature of the associations between visceral malignancies and various subtypes of myositis and scleroderma. Moghadam and colleagues[66,67] in this issue review the relationships, both positive and negative, between myositis syndromes defined not only by their clinical manifestations but also by autoantibody specificities, particularly transcriptional intermediary factor-1-gamma (TIF-1-γ) and nuclear matrix protein-2 (NXP-2) autoantibodies. Also herein, Weeding and colleagues[68–71] elegantly summarize the novel associations linking cancer to the pathophysiology of certain subtypes of systemic sclerosis, particularly the diseases associated with anti-RNA polymerase I/III and anti–RNPC-3. These insights provide an opportunity to dissect the mechanistic links between oncogenesis and the loss of tolerance to tumor-associated antigens and the development of autoimmunity, culminating in these systemic rheumatic diseases.[72] Further, this information provides clinicians with the beginning of a basis to rationally identify patients at high risk for concomitant malignancy for comprehensive cancer screening.[73]

DRUG EFFECTS, CANCER, AND RHEUMATIC DISEASE

Since the initial use of immunosuppressive, disease-modifying medications for RA, there has been concern for the potential adverse effect of cancer. Over the years, many studies and meta-analyses have been undertaken,[3,74–82] a full review of which goes beyond the scope of this overview and is covered elsewhere in this issue. In recent years, the authors have gained confidence that the overall safety of targeted, biologic therapies for RA is excellent with only minimal excess risk of primary or recurrent malignancy.[83] Exceptions remain, of course, and perhaps lymphoma and other hematologic malignancies are the forms of cancer that remain as relative contraindications to certain antirheumatic therapies, particularly tumor necrosis factor (TNF) biologics more so than non-TNF biologics, JAK inhibitors, or conventional synthetic agents. Among patients with lymphoma, B-cell depletion therapy with rituximab maintains its role as the preferred therapeutic option.[84] However, because

power is limited even with large, nationwide register–based studies to detect sparse adverse effects of biologic or targeted therapies, such as malignancies, shared decision making with patients about the potential benefits in relation to the potential harms, including malignancies, is very important. In their thoughtful review of this issue, Pundole and Suarez-Almazor[18] provide a clinically useful summary of available guidelines and commentary about individualizing decision making about antirheumatic therapies and other relevant management strategies in patients with cancer.

The advent and now widespread use of immune checkpoint inhibitor therapy for various cancers heralded an array of rheumatic syndromes, termed rheumatic immune-related adverse effects (rh-irAE), including inflammatory arthritis, polymyalgia, sicca syndrome, myositis, and sclerodermalike syndromes, that occur in 5% to 10% of patients with cancer treated with these agents.[85–89] In some cases, these syndromes have seemed to represent genuine drug-induced rheumatic diseases, fulfilling classification criteria, but other cases have presented atypical features.[90] These syndromes are often severe and can be life threatening. Uma Thanarajasingam and Noha Abdel-Wahab's article, "Immune Checkpoint Inhibition–Does It Cause Rheumatic Diseases? Mechanisms of Cancer-Associated Loss of Tolerance and Pathogenesis of Autoimmunity," in this issue review the literature on this topic in detail, including the pharmacology of immune checkpoint inhibitors, clinical features of rh-irAE, pathophysiology, and clinical management guidelines. rh-irAE seems to result from disinhibiting T-cell regulation, leading to unchecked activation of T-helper (Th) 1 and Th17 cells as well as B cells, driving autoimmunity and tissue inflammation. Many uncertainties remain, particularly the full spectrum of rh-irAE syndromes, similarities and differences of these from idiopathic rheumatic diseases, the underlying molecular mechanisms, ability to identify patients at risk of rh-irAE before immune checkpoint inhibitor therapy, best practices for use of steroids and antirheumatic disease-modifying therapies, and the long-term prognosis, both for the cancer and the rheumatic syndrome.

SUMMARY

When patients present with rheumatic syndromes, it is important to consider the possibility of an underlying or associated malignancy. Age-appropriate and sex-appropriate cancer screening is important for all patients with rheumatic diseases, and more comprehensive screening should be undertaken with consideration of diagnosis, clinical characteristics and serologic findings, disease activity and progression, cancer risk factors, and medication exposures. Elsewhere in this issue, more detailed guidance is presented on cancer screening, such as the risk stratification proposals of Moghadam-Kia and colleagues[91] and Weeding and colleagues.[92] With respect to making decisions with patients about treatment of their rheumatic disease, in general, the evidence is reassuring that the absolute probability of primary or recurrent malignancy is very low (typically, 2–5 per 1000 patients treated for 1 year); in patients with a prior cancer, the risk is especially low when the cancer is inactive and more than 5 years old. The complexity and, sometimes, the uncertainty of the relationship of an individual patient's cancer to the rheumatic disease warrant caution and deliberation by the patient's multidisciplinary team. Several important clinical questions still remain pertaining to cancer and rheumatic disease that require further clinical and translational research.

CLINICS CARE POINTS

- All adult patients with rheumatic diseases should undergo age- and sex-appropriate cancer screening at diagnosis.

- Comprehensive, disease-specific cancer screening is indicated in several higher risk rheumatic diseases, including myositis and systemic sclerosis.
- Effective control of systemic inflammation with disease-modifying antirheumatic drugs is important to mitigate the risk of future cancer in patients with rheumatic diseases.
- Collaborative decision-making between the patient, rheumatologist, and oncologist is crucial when considering treatment of a patient with active malignancy with immunosuppressive therapies.

DISCLOSURE

Dr J.M. Davis has received research grants from Pfizer and has served on advisory boards for Abbvie and Sanofi-Genzyme.

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