HHS Public Access

Author manuscript

Best Pract Res Clin Rheumatol. Author manuscript; available in PMC 2021 February 03.

Published in final edited form as:

Best Pract Res Clin Rheumatol. 2020 February ; 34(1): 101472. doi:10.1016/j.berh.2019.101472.

The relationships between cancer and autoimmune rheumatic diseases

Laura C. Cappelli, MD MHS[1] **[Assistant Professor of Medicine]**, **Ami A. Shah, MD MHS**[2] **[Associate Professor of Medicine]**

[1]Division of Rheumatology, Johns Hopkins University School of Medicine, 5501 Hopkins Bayview Circle, Arthritis Center, Baltimore, MD 21224 USA

[2]Division of Rheumatology, Johns Hopkins University School of Medicine, 5200 Eastern Avenue, Mason F. Lord Center Tower, Suite 4100, Baltimore, MD 21224 USA

Abstract

Links between autoimmune rheumatic diseases and cancer continue to be elucidated. In this review, we explore this complex, bidirectional relationship. First, the increased risk of cancer across the breadth of the autoimmune rheumatic diseases is described. The magnitude of risk and types of tumors seen can differ by type of autoimmune disease, timing of disease course, and even clinical and laboratory features within a particular autoimmune disease, suggesting that targeted cancer screening strategies can be considered. Multiple mechanisms linking autoimmune rheumatic diseases and cancer are discussed, including the development of autoimmunity in the context of naturally occurring anti-tumor immune responses and malignancy arising in the context of inflammation and damage from autoimmunity. Immunosuppression for rheumatic disease can increase risk for certain types of cancers. Finally, immune checkpoint inhibitors, a type of cancer immunotherapy, which cause a variety of inflammatory syndromes of importance to rheumatologists, are reviewed.

Keywords

cancer; autoimmunity; autoantibodies; immune checkpoint inhibitor

Introduction

The relationship between cancer and the autoimmune rheumatic diseases has become increasingly complex. Advances in knowledge of epidemiology, pathogenesis, and long-term outcomes for the rheumatic diseases and the advent of new therapies, both to treat cancer and autoimmune diseases, have uncovered more links between the two entities. In this review, we will focus on several different types of relationships that are relevant to clinical

Address correspondence to: Ami A. Shah, MD MHS, 5200 Eastern Avenue, Mason F. Lord Center Tower, Suite 4100, Baltimore, MD 21224 USA, Ami.Shah@jhmi.edu.

care: rheumatic diseases with increased risk of certain cancers, cancer screening in patients with rheumatic disease, treatments for autoimmunity and their cancer risk, and treatments for cancer and the development of autoimmune/inflammatory syndromes. Throughout, the strengths and limitations in current research and future directions for investigation will be highlighted.

Rheumatic Diseases Associated with Increased Risk of Cancer

Though certain rheumatic diseases, like the inflammatory myopathies, are most recognized for increased rates of malignancy, a wide spectrum of rheumatic diseases have associations with particular types of cancer. The strength of association and types of cancer can vary considerably by disease type. On the other hand, some cancers appear to be increased across multiple autoimmune diseases, like non-Hodgkin lymphoma, which was reported to be associated with 21 different autoimmune diseases in a Swedish registry study[1]. Below we review the risk of cancer across the following rheumatic diseases: idiopathic inflammatory myopathies, systemic sclerosis (scleroderma), rheumatoid arthritis, Sjogren's syndrome, systemic lupus erythematosus (SLE), polymyalgia rheumatica, giant cell arteritis (GCA) and ANCA associated vasculitidies.

Idiopathic Inflammatory Myopathies

Patients with inflammatory myopathies have long been appreciated to have an increased incidence of certain types of cancers[23]. The highest risk for development of cancer is in the three to five years before and after myositis diagnosis[4–6]. Adenocarcinomas are the most commonly associated histological tumor type and may affect the ovaries, GI tract, lung, or breast; squamous head and neck cancers, non-Hodgkin's lymphoma and other malignancies are also reported[748]. The magnitude of cancer risk appears to be related to the subtype of inflammatory myopathy. In one systematic review, patients with dermatomyositis had a 5.5 fold increased risk of cancer while those with polymyositis only had a 1.6 fold increase[7].

Systemic Sclerosis (Scleroderma)

As a population, patients with scleroderma also have an increased risk of cancer, with standardized incidence ratios (SIRs) ranging from 1.24–4.20[9–17]. Tumor types that are seen at a higher risk than that expected in the general population include lung, liver, esophageal, oral cavity, thyroid, melanoma, non-melanoma skin and hematologic malignancies. Recent data have demonstrated that the risk for specific tumor types may vary depending on scleroderma disease duration, autoantibody type and cutaneous subset[18] (see section entitled, "Risk stratifying within diseases"). For instance, while most studies have not demonstrated an increased risk of breast cancer in patients with scleroderma, recent data demonstrate that the risk of breast cancer is markedly elevated around the time of scleroderma onset among patients with diffuse scleroderma and RNA polymerase III antibodies.

Rheumatoid arthritis

Patients with rheumatoid arthritis (RA) have a slightly higher incidence of any malignancy than the general population, with rates of lymphoma and lung cancer the most increased[1920]

(standardized incidence ratios of 2.46 and 1.64 respectively in a recent systematic review)[20]. The rates of colon cancer, conversely, may be lower in RA patients than the general population[20].

Sjogren's syndrome

Overall cancer risk is higher in Sjogren's syndrome than the general population with a risk ratio of 1.53 in one systematic review[21]. Non Hodgkin's lymphoma is particularly increased, 13 to 18 times the rate in the general population[2122]. These are primarily B cell lymphomas and can be found in the mucosa-associated lymphoid tissue (MALT lymphoma) or elsewhere[23]. An increased risk of thyroid cancer can also be seen[21].

Systemic lupus erythematosus

The overall risk of developing any malignancy in patients with SLE is slightly higher than that of the general population (SIR 1.14–1.28 for all cancer types)[24–26]. As in primary Sjogren's syndrome, rates of non-Hodgkin lymphoma are increased in SLE[22242728]. Additionally, rates of HPV-associated cancers, such as cervical and vulvar cancer, have been elevated across multiple large cohort studies[2427–29]. Interestingly, patients with SLE have a lower risk of breast cancer and prostate cancer compared to that expected in the general population[242527].

Polymyalgia rheumatica/Giant Cell Arteritis

Similar to SLE and RA, patients with giant cell arteritis (GCA) and polymyalgia rheumatica (PMR) have only a slightly increased risk of cancer. A systematic review of cohort studies showed a risk ratio of 1.14 for any malignancy in patients with GCA/PMR[30]. The same study also demonstrated a higher cancer risk in the first 6–12 months after GCA/PMR diagnosis.

ANCA Vasculitis

Standardized incidence ratios for cancer in ANCA associated vasculitis range from 1.6 to 2 in most studies[31]. Many studies have focused on granulomatosis with polyangiitis (GPA) rather than microscopic polyangiitis. In studies that include the two phenotypes, however, GPA appears to have a higher risk of cancer[31]. As discussed later in the review, treatment related factors in ANCA vasculitis may play a significant role in risk of particular tumor types, including cancers of the urinary tract, leukemia and non-melanoma skin cancer.

Mechanisms to explain increased cancer risk in autoimmune disease

There are several mechanisms that may contribute to the increased risk of cancers in patients with autoimmune rheumatic disease, as summarized in Table 1[32]. One theory is that naturally occurring immune responses against cancer can trigger autoimmunity and rheumatic disease[33]. Clinical data in support of this hypothesis include short interval cancer development in dermatomyositis and scleroderma; that is, there are subsets of patients in both autoimmune diseases who develop cancer and their autoimmune disease within less than three years of each other suggesting that the pathogenesis is related. In both diseases, patients with a higher risk of cancer around rheumatic disease onset can be identified by the

presence of distinct autoantibodies. In scleroderma, patients with anti-RNA polymerase III or anti-RNPC3 antibodies have a significantly increased risk of cancer-associated scleroderma[1834–37]. Similarly, dermatomyositis patients with anti-TIF1gamma or anti-NXP2 antibodies have a higher risk of cancer-associated myositis[38]. Mechanistic data suggest a model of cancer-induced autoimmunity in these patients, in which mutated self antigens in tumors are seen as foreign by the immune system and trigger mutation-specific cellular and cross-reactive humoral immune responses[33]. In scleroderma, several patients with antibodies to RNA polymerase III were found to have genetic alterations in POLR3A in their tumors (somatic mutations and/or loss of heterozygosity) while those without RNA polymerase III antibodies did not have these genetic alterations[39]. Similarly in a study of dermatomyositis patients, those with anti-TIF1gamma antibodies had mutations of the TIF1gamma gene in their tumors while the majority of patients without anti-TIF1gamma antibodies did not[40].

In patients where rheumatic disease precedes cancer development, inflammation and tissue damage from chronic autoimmunity may lead to malignancy. In RA, patients with elevated inflammatory markers had increased cancer risk in one study[41]. Conversely, RA patients treated with corticosteroid therapy chronically or for flares were less likely to develop lymphoma in a case-control study[42]. In Sjogren's syndrome, having a higher EULAR Sjogren Syndrome Disease Activity Index at time of diagnosis has been associated with increased lymphoma risk[23]. Patients with scleroderma-associated ILD also have an increased risk of lung cancer in the affected target tissue[4344]. Additionally, inability to clear viral infections may predispose patients with autoimmune disease to cancer. In SLE, risk of certain cancers, like human papillomavirus-associated tumors, appears to be increased[45]. Possible mechanisms underpinning the links between treatment for either rheumatic diseases or cancer, and risk of developing the other disease, will be discussed in detail later.

Cancer Screening and Surveillance in patients with Rheumatic Diseases

In patients with new onset rheumatic disease, particularly those who are older, or who have atypical/aggressive disease features or have an autoantibody subset where a mechanism of cancer-induced autoimmunity is likely[35], an important question is the optimal approach to detect an underlying malignancy. There is a paucity of studies evaluating cancer screening in the rheumatic diseases. In a prospective study of dermatomyositis and polymyositis, 55 patients were screened by whole body positron emission tomography (PET)/CT and by conventional screenings (CT of the chest and abdomen, mammography, gynecologic examination, pelvic ultrasonography, and tumor marker analysis) with comparable positive and negative predictive values for the diagnosis of cancer with both modalities[46]. The authors concluded that a single PET/CT may be sufficient to screen patients with new onset myositis for cancer. A later retrospective study in multiple forms of myositis, including dermatomyositis, anti-synthetase syndrome and immune mediated necrotizing myopathy, of PET/CT versus conventional cancer screening showed no difference in detection of cancer but there were additional biopsies in the PET group suggesting the risk of false positives with PET as a screening test[47]. Another study evaluated cost of PET/CT versus conventional screening and demonstrated that patients incurred less cost for the PET/CT scan than conventional screenings, while insurers had a higher cost[48]. Similar data evaluating cancer screening strategies in other rheumatic diseases are lacking.

Risk stratifying within diseases

Within a population of patients with scleroderma, data suggest that the optimal cancer detection strategy may vary depending on specific autoantibody and phenotypic subsets[18]. For instance, patients with scleroderma, RNA polymerase III antibodies and diffuse cutaneous disease have a markedly increased risk of breast, prostate and tongue cancer whereas those with RNA polymerase III antibodies and limited cutaneous disease have a higher risk of lung cancer. Among scleroderma patients who are negative for centromere, topoisomerase 1 and RNA polymerase III antibodies, there is a higher risk of breast cancer and melanoma in those with limited scleroderma and a higher risk of tongue cancer in diffuse scleroderma. Interestingly, patients with anti-centromere antibodies have a lower risk of cancer than that expected in the general population, suggesting age, sex and risk factor appropriate cancer screening alone may be sufficient within defined subgroups. These data raise the question of whether cancer screening strategies can be targeted to unique disease subsets in these diseases; further work is necessary to validate this in both scleroderma and dermatomyositis.

In dermatomyositis, TIF1gamma and NXP2 antibodies are most associated with increased risk of malignancy[3849–51]. For anti-TIF1 antibody positive patients, they were more likely to have short interval cancer (less than 3 years before or after myositis diagnosis) and more likely to have ovarian cancer[6]. In Sjogren's syndrome, several clinical features and laboratory findings are associated with the development of hematologic malignancies, most commonly MALT and non-MALT lymphomas. These include evidence of disease activity at diagnosis, parotid gland enlargement, lymphadenopathy, splenomegaly, presence of cryoglobulins, cytopenias, and low complement levels[2352]. The same features were not associated with increased risk for solid tumors in one study[23].

In SLE, short disease duration appears to be associated with development of lymphoma, while lung cancer and skin cancer may be later manifestations[25]. Other potential risk factors like particular immunosuppressive agents require further study to define their role. EULAR recommends cervical cancer screening in SLE patients who are "heavily immunosuppressed" with Pap smears once a year, otherwise they recommend following standard screening protocols[53].

Clinicians may consider more aggressive cancer screening than age-based in patients with any of these high-risk clinical features (Table 2). There is not good evidence, however, about specific ways to enhance screening in patients with rheumatic diseases, so recommendations are based on clinical experience.

Treatments for Rheumatic Disease and Development of Cancer

Several medications commonly used in rheumatic diseases are associated with a higher risk of cancer. An increased risk of malignancy is well documented in patients treated with cyclophosphamide. In granulomatosis with polyangiitis, the risk of both bladder cancer and leukemia increases with cumulative dose of cyclophosphamide[5455]. Patients who received cumulative doses greater than 36 g were at highest risk for bladder cancer and acute myeloid leukemia[55]. Smoking and prior episodes of hemorrhagic cystitis were predictive of urinary

tract cancer in patients with vasculitis (including, but not limited to, granulomatosis with polyangiitis)[56]. In SLE, cervical intraepithelial neoplasia may be increased in those treated with IV cyclophosphamide[57].

Other immunosuppressive drugs like mycophenolate and azathioprine are commonly used in rheumatology, but their risk of malignancy is better studied in patients who have undergone organ transplantation. The data is conflicting on whether mycophenolate is associated with increased risk of lymphoproliferative diseases and non-melanoma skin cancer[58–61]. In one heart transplant study it appeared that mycophenolate was actually associated with a lower risk of malignancy compared to other regimens[62]. Azathioprine does seem to be associated with development of cutaneous squamous cell carcinoma after transplant[63]. Interestingly, one study showed decreased incidence of cutaneous squamous cell carcinoma when lung transplant patients switched from azathioprine to mycophenolate[64].

Methotrexate is commonly used across the rheumatic diseases and has been associated with non-melanoma skin cancer in RA, psoriasis, and psoriatic arthritis[65]. A large study of low dose methotrexate for prevention of cardiovascular disease showed an increased risk of non-melanoma skin cancer in the methotrexate group as compared to placebo[66].

The largest studies of TNF-inhibitors and other monoclonal antibodies used to treat autoimmune disease come from the RA literature. Several studies from large registries in Europe and Australia have evaluated risk of developing various cancers in RA patients exposed to different biologic therapies[67–70]. In one study with several European registries, the risk of melanoma was compared to background risk for country of residence and was found not to be increased for patients on TNF-inhibitors, abatacept, tocilizumab, or rituximab.[67] Similar results have been seen for both lymphoma and solid tumors in the British biologics registry[6869]. The risk of non-melanoma skin cancer, however, is reported to be increased with TNF-inhibitor therapy in RA and psoriasis[65].

Given the increase of non-melanoma skin cancer with a variety of treatments for rheumatic disease, it is important to counsel patients on sun protection. Patients on methotrexate, TNF-inhibitors, azathioprine and mycophenolate should wear sun protective clothing or sunblock with UVA/UVB coverage, and be advised to report promptly any new persistent skin lesions, or change in appearance of existing skin lesions. Full body skin examinations by a dermatologist/enrollment in a skin cancer screening program may be appropriate for some patients.

Cancer history and immunosuppression

The question of how to treat patients with autoimmune disease and previous cancers is also important for clinicians. There has been a theoretical concern that biologics and other immunosuppressive agents like mycophenolate may impair immune responses to tumors leading to a reluctance of clinicians to use these drugs in patients with a history of or active cancer. Recent guidelines for rheumatoid arthritis have recommended not using biologics (except rituximab) in patients with a history of lymphoproliferative disorders and to use csDMARDs over biologics in melanoma and non-melanoma skin cancer[71]. In a registry study and a recent systematic review, however, patients with previous cancer treated

subsequently with biologics had no increased risk of new or recurrent cancer when compared to patients who received csDMARDs[7273].

Cancer therapies and development/exacerbation of rheumatic disease

Chemotherapy and targeted therapies

A variety of chemotherapeutic agents, including bleomycin, gemcitabine, carboplatin and paclitaxel, have been associated with scleroderma-like disease, Raynaud's phenomenon, and/or critical digital ischemia[74–79]. Aromatase inhibitors, used in hormone receptor positive breast cancer, are well known to cause arthralgia which is a class effect and not increased for any particular medication[80]. Notably, up to 20% of patients will not adhere to aromatase inhibitors due to joint pain[81].

Radiation

Radiation, particularly of the head and neck, can lead to xerostomia which may be similar to that of primary Sjogren's syndrome. Radiation may also trigger de novo fibrosing syndromes such as localized scleroderma (morphea). Many studies have also investigated whether use of radiation therapy is safe in patients with pre-existing rheumatic disease. The concern has been greatest in scleroderma, as radiation may trigger exaggerated fibrosis. A recent study examining use of radiation therapy for breast cancer in scleroderma patients suggests that up to 50% of patients may develop skin thickening in the radiation port[82]. In a limited sample size, however, there was no evidence that radiation therapy triggered systemic disease flares such as worsening of generalized skin thickening or significant interstitial lung disease.

Immune Checkpoint Inhibitors and Rheumatic Disease

The use of cancer immunotherapy has grown tremendously over the last decade. There are several types of immunotherapies including chimeric antigen receptor (CAR) T cells, cancer vaccines, high dose IL-2 infusions and immune checkpoint inhibitors (ICIs)[83]. By far, ICIs are the most commonly used immunotherapy and their applications continue to increase[84]. ICIs block inhibitory interactions to allow for unchecked activation of T cells[85]. Blocking immune checkpoints is not a tumor specific approach and is effective in a wide variety of malignancies. Due to the unopposed activation of T cells, however, inflammatory syndromes can develop known as immune related adverse events (irAEs)[86].

IrAEs may affect almost any organ from the skin, endocrine glands, the GI tract, heart, lungs and the nervous system[87]. There are several irAEs with phenotypes similar to classic rheumatologic diseases. These include inflammatory arthritis[88–94], sicca syndrome[8995–97], polymyalgia rheumatica[9899], giant cell arteritis[100101], myositis[102–106], scleroderma[107108], anti-neutrophil cytoplasmic antibody-associated vasculitis[109110], aortitis[111], and eosinophilic fasciitis[112]. Subacute cutaneous lupus has been described[113114] as has a case of isolated lupus nephritis[115], but no other systemic manifestations of SLE have been reported.

There are some key differences between rheumatic irAEs and traditional forms of rheumatic disease. There is a low rate of seropositivity for RF and anti-CCP antibodies in those with

inflammatory arthritis and a low rate of anti-Ro or La positivity in those with sicca syndrome[89949597116]. Unlike most rheumatic diseases, irAEs can be self-limited and resolve after the ICI is withdrawn, though inflammatory arthritis appears to persist in a large subset of patients[116].

Treating rheumatic irAEs

Prospective studies describing the treatment of rheumatic irAEs have been limited. One study of patients with ICI-induced inflammatory arthritis showed that 75% of patients referred to rheumatology needed some kind of immunosuppression[116]. In this study, there was no difference in rates of tumor progression in those treated or untreated with csDMARDs or biologics[116]. The timing of immunosuppression may be important. Multiple studies in melanoma and other tumors have shown no worsening of tumor response when irAEs are treated with steroids or even short term TNF-inhibition[117–120]. On the other hand, patients with non small cell lung cancer who were on 10 mg prednisone or higher at the start of ICI therapy had a worse response than those on lower dose or no prednisone[121]. A description of treatment modalities used in rheumatic irAEs is detailed in Table 3.

Preexisting autoimmune disease and ICI therapy

With ICIs becoming standard of care for an increasing number of cancers, oncologists and rheumatologists must decide whether to treat patients with known autoimmune disease with these drugs. As patients with preexisting autoimmune disease were excluded from clinical trials, data comes primarily from retrospective observational studies. A systematic literature review of observational studies including case reports showed that flare of autoimmune disease was common, but most were managed with corticosteroids and did not require discontinuation of ICI therapy[122]. A wide variety of autoimmune disease were included such as RA, psoriatic arthritis/psoriasis, autoimmune thyroid disease, inflammatory bowel disease, sarcoid, and SLE; psoriatic arthritis/psoriasis and RA were the largest groups in the study. Fifty percent of patients overall had an exacerbation of their underlying autoimmune disease; 64% of psoriasis patients had a worsening of skin disease and 50% of RA patients had a flare of joint disease[122].

Concurrent immunomodulatory medications are sometimes used in patients with autoimmune disease requiring ICI therapy for cancer. Medications reported in the literature include corticosteroids, conventional synthetic disease modifying anti-rheumatic drugs (DMARDs) like hydroxychloroquine and methotrexate, and biologic DMARDs like TNF-inhibitors[122]. The ideal approach is not yet defined given the limited available data. In fact, there is no comprehensive study to provide guidance or that documents how the use of DMARDs or corticosteroids affects tumor response to ICI therapy. Current research is underway. There is an ongoing trial to evaluate the use of anti-PD-1 therapy in patients with preexisting autoimmune disease and malignancies for which anti-PD-1 has shown efficacy[123].

Summary

Understanding of the many biologic connections between autoimmune rheumatic diseases and malignancies continues to evolve. Most autoimmune rheumatic diseases are associated with a small increased risk of cancer as compared to the general population. The magnitude of risk varies considerably and is highest in dermatomyositis. Mechanisms explaining the links between certain cancers and autoimmune disease are not fully elucidated. Compelling evidence supports the concept that an immune response against cancer triggers autoimmunity. Clinical experience suggests that chronic inflammation and damage from autoimmune disease can trigger the development of cancer. Certain high-risk groups within rheumatic diseases may benefit from more intensive cancer screening, such as dermatomyositis patients with NXP-2 or TIF1gamma autoantibodies or scleroderma patients with anti-RNA polymerase III or anti-RNPC3 antibodies. Agents used as treatments for rheumatic disease can also increase the risk of cancer. Cyclophosphamide is associated with bladder cancer and leukemia, while azathioprine, methotrexate, and TNF-inhibitors have shown an increased risk of skin cancer. Patients who undergo treatment for malignancies may also experience either worsening of their rheumatic disease or new syndromes that are similar to traditional rheumatic diseases. Most notable has been the immune checkpoint inhibitors, which can cause a wide variety of inflammatory side effects that mimic rheumatic disease. Further work probing this complex cancer-autoimmunity interface is likely to improve our understanding of mechanisms and treatment strategies important for both anti-tumor immunity and autoimmunity.

Conflict of interest and funding statement:

LCC has received research funding from Bristol-Myers Squibb and has been a consultant for Regeneron/Sanofi. AAS has been a consultant for Bristol-Myers Squibb.

LCC was supported by NIH/NIAMS K23-AR075872 and an investigator initiated grant from Bristol-Myers Squibb. AAS was supported by NIH/NIAMS R01- AR073208. Both authors were supported by NIAMS P30-AR070254. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health.

References

1. Fallah M, Liu X, Ji J, et al. Autoimmune diseases associated with non-Hodgkin lymphoma: a nationwide cohort study. Annals of oncology : official journal of the European Society for Medical Oncology 2014;25(10):2025–30. [PubMed: 25081899]
2. Kankelheit H Uber primare nichteitrige Polymyositis. Dtsch Arch Klin Med;120:335–49.
3. Barnes BE, Mawr B. Dermatomyositis and malignancy. A review of the literature. Annals of internal medicine 1976;84(1):68–76. [PubMed: 1106291]
4. Sigurgeirsson B, Lindelof B, Edhag O, et al. Risk of cancer in patients with dermatomyositis or polymyositis. A population-based study. The New England journal of medicine 1992;326(6):363–7. [PubMed: 1729618]
5. Chen YJ, Wu CY, Huang YL, et al. Cancer risks of dermatomyositis and polymyositis: a nationwide cohort study in Taiwan. Arthritis research & therapy 2010;12(2):R70. [PubMed: 20398365]
6. Oldroyd A, Sergeant JC, New P, et al. The temporal relationship between cancer and adult onset anti-transcriptional intermediary factor 1 antibody-positive dermatomyositis. Rheumatology (Oxford, England) 2019;58(4):650–55.
7. Yang Z, Lin F, Qin B, et al. Polymyositis/dermatomyositis and malignancy risk: a metaanalysis study. The Journal of rheumatology 2015;42(2):282–91. [PubMed: 25448790]

8. Hill CL, Zhang Y, Sigurgeirsson B, et al. Frequency of specific cancer types in dermatomyositis and polymyositis: a population-based study. Lancet (London, England) 2001;357(9250):96–100.
9. Roumm AD, Medsger TA Jr. Cancer and systemic sclerosis. An epidemiologic study. Arthritis and rheumatism 1985;28(12):1336–40. [PubMed: 4084328]
10. Abu-Shakra M, Guillemin F, Lee P. Cancer in systemic sclerosis. Arthritis and rheumatism 1993;36(4):460–4. [PubMed: 8457221]
11. Rosenthal AK, McLaughlin JK, Linet MS, et al. Scleroderma and malignancy: an epidemiological study. Annals of the rheumatic diseases 1993;52(7):531–3. [PubMed: 8346981]
12. Rosenthal AK, McLaughlin JK, Gridley G, et al. Incidence of cancer among patients with systemic sclerosis. Cancer 1995;76(5):910–4. [PubMed: 8625197]
13. Hill CL, Nguyen AM, Roder D, et al. Risk of cancer in patients with scleroderma: a population based cohort study. Annals of the rheumatic diseases 2003;62(8):728–31. [PubMed: 12860727]
14. Derk CT, Rasheed M, Artlett CM, et al. A cohort study of cancer incidence in systemic sclerosis. The Journal of rheumatology 2006;33(6):1113–6. [PubMed: 16622904]
15. Kang KY, Yim HW, Kim IJ, et al. Incidence of cancer among patients with systemic sclerosis in Korea: results from a single centre. Scandinavian journal of rheumatology 2009;38(4):299–303. [PubMed: 19308805]
16. Olesen AB, Svaerke C, Farkas DK, et al. Systemic sclerosis and the risk of cancer: a nationwide population-based cohort study. The British journal of dermatology 2010;163(4):800–6. [PubMed: 20854403]
17. Siau K, Laversuch CJ, Creamer P, et al. Malignancy in scleroderma patients from south west England: a population-based cohort study. Rheumatology international 2011;31(5):641–5. [PubMed: 20058012]
18. Igusa T, Hummers LK, Visvanathan K, et al. Autoantibodies and scleroderma phenotype define subgroups at high-risk and low-risk for cancer. Annals of the rheumatic diseases 2018;77(8):1179–86. [PubMed: 29678941]
19. Smitten AL, Simon TA, Hochberg MC, et al. A meta-analysis of the incidence of malignancy in adult patients with rheumatoid arthritis. Arthritis research & therapy 2008;10(2):R45. [PubMed: 18433475]
20. Simon TA, Thompson A, Gandhi KK, et al. Incidence of malignancy in adult patients with rheumatoid arthritis: a meta-analysis. Arthritis research & therapy 2015;17:212. [PubMed: 26271620]
21. Liang Y, Yang Z, Qin B, et al. Primary Sjogren's syndrome and malignancy risk: a systematic review and meta-analysis. Annals of the rheumatic diseases 2014;73(6):1151–6. [PubMed: 23687261]
22. Zintzaras E, Voulgarelis M, Moutsopoulos HM. The risk of lymphoma development in autoimmune diseases: a meta-analysis. Archives of internal medicine 2005;165(20):2337–44. [PubMed: 16287762]
23. Brito-Zeron P, Kostov B, Fraile G, et al. Characterization and risk estimate of cancer in patients with primary Sjogren syndrome. Journal of hematology & oncology 2017;10(1):90. [PubMed: 28416003]
24. Bernatsky S, Ramsey-Goldman R, Labrecque J, et al. Cancer risk in systemic lupus: an updated international multi-centre cohort study. Journal of autoimmunity 2013;42:130–5. [PubMed: 23410586]
25. Bjornadal L, Lofstrom B, Yin L, et al. Increased cancer incidence in a Swedish cohort of patients with systemic lupus erythematosus. Scandinavian journal of rheumatology 2002;31(2):66–71. [PubMed: 12109649]
26. Song L, Wang Y, Zhang J, et al. The risks of cancer development in systemic lupus erythematosus (SLE) patients: a systematic review and meta-analysis. Arthritis research & therapy 2018;20(1):270. [PubMed: 30522515]
27. Chen YJ, Chang YT, Wang CB, et al. Malignancy in systemic lupus erythematosus: a nationwide cohort study in Taiwan. The American journal of medicine 2010;123(12):1150.e1–6.

28. Parikh-Patel A, White RH, Allen M, et al. Cancer risk in a cohort of patients with systemic lupus erythematosus (SLE) in California. Cancer causes & control : CCC 2008;19(8):887–94. [PubMed: 18386139]
29. Nath R, Mant C, Luxton J, et al. High risk of human papillomavirus type 16 infections and of development of cervical squamous intraepithelial lesions in systemic lupus erythematosus patients. Arthritis and rheumatism 2007;57(4):619–25. [PubMed: 17471531]
30. Ungprasert P, Sanguankeo A, Upala S, et al. Risk of malignancy in patients with giant cell arteritis and polymyalgia rheumatica: a systematic review and meta-analysis. Seminars in arthritis and rheumatism 2014;44(3):366–70. [PubMed: 25074657]
31. Mahr A, Heijl C, Le Guenno G, et al. ANCA-associated vasculitis and malignancy: current evidence for cause and consequence relationships. Best practice & research Clinical rheumatology 2013;27(1):45–56. [PubMed: 23507056]
32. Egiziano G, Bernatsky S, Shah AA. Cancer and autoimmunity: Harnessing longitudinal cohorts to probe the link. Best practice & research Clinical rheumatology 2016;30(1):53–62. [PubMed: 27421216]
33. Shah AA, Casciola-Rosen L, Rosen A. Review: cancer-induced autoimmunity in the rheumatic diseases. Arthritis & rheumatology (Hoboken, NJ) 2015;67(2):317–26.
34. Xu GJ, Shah AA, Li MZ, et al. Systematic autoantigen analysis identifies a distinct subtype of scleroderma with coincident cancer. Proceedings of the National Academy of Sciences of the United States of America 2016;113(47):E7526–e34. [PubMed: 27821747]
35. Shah AA, Hummers LK, Casciola-Rosen L, et al. Examination of autoantibody status and clinical features associated with cancer risk and cancer-associated scleroderma. Arthritis & rheumatology (Hoboken, NJ) 2015;67(4):1053–61.
36. Shah AA, Rosen A, Hummers L, et al. Close temporal relationship between onset of cancer and scleroderma in patients with RNA polymerase I/III antibodies. Arthritis and rheumatism 2010;62(9):2787–95. [PubMed: 20506513]
37. Shah AA, Xu G, Rosen A, et al. Brief Report: Anti-RNPC-3 Antibodies As a Marker of Cancer-Associated Scleroderma. Arthritis & rheumatology (Hoboken, NJ) 2017;69(6):1306–12.
38. Fiorentino DF, Chung LS, Christopher-Stine L, et al. Most patients with cancer-associated dermatomyositis have antibodies to nuclear matrix protein NXP-2 or transcription intermediary factor 1gamma. Arthritis and rheumatism 2013;65(11):2954–62. [PubMed: 24037894]
39. Joseph CG, Darrah E, Shah AA, et al. Association of the autoimmune disease scleroderma with an immunologic response to cancer. Science (New York, NY) 2014;343(6167):152–7.
40. Pinal-Fernandez I, Ferrer-Fabregas B, Trallero-Araguas E, et al. Tumour TIF1 mutations and loss of heterozygosity related to cancer-associated myositis. Rheumatology (Oxford, England) 2018;57(2):388–96.
41. Llorca J, Lopez-Diaz MJ, Gonzalez-Juanatey C, et al. Persistent chronic inflammation contributes to the development of cancer in patients with rheumatoid arthritis from a defined population of northwestern Spain. Seminars in arthritis and rheumatism 2007;37(1):31–8. [PubMed: 17360028]
42. Hellgren K, Iliadou A, Rosenquist R, et al. Rheumatoid arthritis, treatment with corticosteroids and risk of malignant lymphomas: results from a case-control study. Annals of the rheumatic diseases 2010;69(4):654–9. [PubMed: 19439429]
43. Pontifex EK, Hill CL, Roberts-Thomson P. Risk factors for lung cancer in patients with scleroderma: a nested case-control study. Annals of the rheumatic diseases 2007;66(4):551–3. [PubMed: 16984943]
44. Colaci M, Giuggioli D, Sebastiani M, et al. Lung cancer in scleroderma: results from an Italian rheumatologic center and review of the literature. Autoimmunity reviews 2013;12(3):374–9. [PubMed: 22743031]
45. Dreyer L, Faurschou M, Mogensen M, et al. High incidence of potentially virus-induced malignancies in systemic lupus erythematosus: a long-term followup study in a Danish cohort. Arthritis and rheumatism 2011;63(10):3032–7. [PubMed: 21953088]
46. Selva-O'Callaghan A, Grau JM, Gamez-Cenzano C, et al. Conventional cancer screening versus PET/CT in dermatomyositis/polymyositis. The American journal of medicine 2010;123(6):558–62. [PubMed: 20569766]

47. Maliha PG, Hudson M, Abikhzer G, et al. 18F-FDG PET/CT versus conventional investigations for cancer screening in autoimmune inflammatory myopathy in the era of novel myopathy classifications. Nuclear medicine communications 2019;40(4):377–82. [PubMed: 30664602]
48. Kundrick A, Kirby J, Ba D, et al. Positron emission tomography costs less to patients than conventional screening for malignancy in dermatomyositis. Seminars in arthritis and rheumatism 2019;49(1):140–44. [PubMed: 30482435]
49. Yang H, Peng Q, Yin L, et al. Identification of multiple cancer-associated myositis-specific autoantibodies in idiopathic inflammatory myopathies: a large longitudinal cohort study. Arthritis research & therapy 2017;19(1):259. [PubMed: 29178913]
50. Fujimoto M, Hamaguchi Y, Kaji K, et al. Myositis-specific anti-155/140 autoantibodies target transcription intermediary factor 1 family proteins. Arthritis and rheumatism 2012;64(2):513–22. [PubMed: 21987216]
51. Albayda J, Pinal-Fernandez I, Huang W, et al. Antinuclear Matrix Protein 2 Autoantibodies and Edema, Muscle Disease, and Malignancy Risk in Dermatomyositis Patients. Arthritis care & research 2017;69(11):1771–76. [PubMed: 28085235]
52. Nishishinya MB, Pereda CA, Munoz-Fernandez S, et al. Identification of lymphoma predictors in patients with primary Sjogren's syndrome: a systematic literature review and meta-analysis. Rheumatology international 2015;35(1):17–26. [PubMed: 24899571]
53. Andreoli L, Bertsias GK, Agmon-Levin N, et al. EULAR recommendations for women's health and the management of family planning, assisted reproduction, pregnancy and menopause in patients with systemic lupus erythematosus and/or antiphospholipid syndrome. Annals of the rheumatic diseases 2017;76(3):476–85. [PubMed: 27457513]
54. Knight A, Askling J, Granath F, et al. Urinary bladder cancer in Wegener's granulomatosis: risks and relation to cyclophosphamide. Annals of the rheumatic diseases 2004;63(10):1307–11. [PubMed: 15130900]
55. Faurschou M, Sorensen IJ, Mellemkjaer L, et al. Malignancies in Wegener's granulomatosis: incidence and relation to cyclophosphamide therapy in a cohort of 293 patients. The Journal of rheumatology 2008;35(1):100–5. [PubMed: 17937462]
56. Le Guenno G, Mahr A, Pagnoux C, et al. Incidence and predictors of urotoxic adverse events in cyclophosphamide-treated patients with systemic necrotizing vasculitides. Arthritis and rheumatism 2011;63(5):1435–45. [PubMed: 21337321]
57. Ognenovski VM, Marder W, Somers EC, et al. Increased incidence of cervical intraepithelial neoplasia in women with systemic lupus erythematosus treated with intravenous cyclophosphamide. The Journal of rheumatology 2004;31(9):1763–7. [PubMed: 15338497]
58. Robson R, Cecka JM, Opelz G, et al. Prospective registry-based observational cohort study of the long-term risk of malignancies in renal transplant patients treated with mycophenolate mofetil. American journal of transplantation : official journal of the American Society of Transplantation and the American Society of Transplant Surgeons 2005;5(12):2954–60.
59. Bichari W, Bartiromo M, Mohey H, et al. Significant risk factors for occurrence of cancer after renal transplantation: a single center cohort study of 1265 cases. Transplantation prssoceedings 2009;41(2):672–3.
60. Marcen R, Galeano C, Fernandez-Rodriguez A, et al. Effects of the new immunosuppressive agents on the occurrence of malignancies after renal transplantation. Transplantation proceedings 2010;42(8):3055–7. [PubMed: 20970609]
61. Crane GM, Powell H, Kostadinov R, et al. Primary CNS lymphoproliferative disease, mycophenolate and calcineurin inhibitor usage. Oncotarget 2015;6(32):33849–66. [PubMed: 26460822]
62. O'Neill JO, Edwards LB, Taylor DO. Mycophenolate mofetil and risk of developing malignancy after orthotopic heart transplantation: analysis of the transplant registry of the International Society for Heart and Lung Transplantation. The Journal of heart and lung transplantation : the official publication of the International Society for Heart Transplantation 2006;25(10):1186–91.
63. Sanders ML, Karnes JH, Denny JC, et al. Clinical and Genetic Factors Associated with Cutaneous Squamous Cell Carcinoma in Kidney and Heart Transplant Recipients. Transplantation direct 2015;1(4).

64. Vos M, Plasmeijer EI, van Bemmel BC, et al. Azathioprine to mycophenolate mofetil transition and risk of squamous cell carcinoma after lung transplantation. The Journal of heart and lung transplantation : the official publication of the International Society for Heart Transplantation 2018;37(7):853–59.

65. Krathen MS, Gottlieb AB, Mease PJ. Pharmacologic immunomodulation and cutaneous malignancy in rheumatoid arthritis, psoriasis, and psoriatic arthritis. The Journal of rheumatology 2010;37(11):2205–15. [PubMed: 20810498]

66. Ridker PM, Everett BM, Pradhan A, et al. Low-Dose Methotrexate for the Prevention of Atherosclerotic Events. The New England journal of medicine 2019;380(8):752–62. [PubMed: 30415610]

67. Mercer LK, Askling J, Raaschou P, et al. Risk of invasive melanoma in patients with rheumatoid arthritis treated with biologics: results from a collaborative project of 11 European biologic registers. Annals of the rheumatic diseases 2017;76(2):386–91. [PubMed: 27307502]

68. Mercer LK, Galloway JB, Lunt M, et al. Risk of lymphoma in patients exposed to antitumour necrosis factor therapy: results from the British Society for Rheumatology Biologics Register for Rheumatoid Arthritis. Annals of the rheumatic diseases 2016.

69. Mercer LK, Lunt M, Low AL, et al. Risk of solid cancer in patients exposed to anti-tumour necrosis factor therapy: results from the British Society for Rheumatology Biologics Register for Rheumatoid Arthritis. Annals of the rheumatic diseases 2015;74(6):1087–93. [PubMed: 24685910]

70. Staples MP, March L, Hill C, et al. Malignancy risk in Australian rheumatoid arthritis patients treated with anti-tumour necrosis factor therapy: an update from the Australian Rheumatology Association Database (ARAD) prospective cohort study. BMC rheumatology 2019;3:1.

71. Singh JA, Saag KG, Bridges SL Jr., et al. 2015 American College of Rheumatology Guideline for the Treatment of Rheumatoid Arthritis. Arthritis care & research 2016;68(1):1–25. [PubMed: 26545825]

72. Xie W, Xiao S, Huang Y, et al. A meta-analysis of biologic therapies on risk of new or recurrent cancer in patients with rheumatoid arthritis and a prior malignancy. Rheumatology (Oxford, England) 2019.

73. Silva-Fernandez L, Lunt M, Kearsley-Fleet L, et al. The incidence of cancer in patients with rheumatoid arthritis and a prior malignancy who receive TNF inhibitors or rituximab: results from the British Society for Rheumatology Biologics Register-Rheumatoid Arthritis. Rheumatology (Oxford, England) 2016;55(11):2033–39.

74. Clowse ME, Wigley FM. Digital necrosis related to carboplatin and gemcitabine therapy in systemic sclerosis. The Journal of rheumatology 2003;30(6):1341–3. [PubMed: 12784412]

75. Bessis D, Guillot B, Legouffe E, et al. Gemcitabine-associated scleroderma-like changes of the lower extremities. Journal of the American Academy of Dermatology 2004;51(2 Suppl):S73–6. [PubMed: 15280817]

76. Yamada Y, Suzuki K, Nobata H, et al. Gemcitabine-induced hemolytic uremic syndrome mimicking scleroderma renal crisis presenting with Raynaud's phenomenon, positive antinuclear antibodies and hypertensive emergency. Internal medicine (Tokyo, Japan) 2014;53(5):445–8.

77. Inaoki M, Kawabata C, Nishijima C, et al. Case of bleomycin-induced scleroderma. The Journal of dermatology 2012;39(5):482–4. [PubMed: 21955042]

78. Kerr LD, Spiera H. Scleroderma in association with the use of bleomycin: a report of 3 cases. The Journal of rheumatology 1992;19(2):294–6. [PubMed: 1378497]

79. De Angelis R, Bugatti L, Cerioni A, et al. Diffuse scleroderma occurring after the use of paclitaxel for ovarian cancer. Clinical rheumatology 2003;22(1):49–52. [PubMed: 12605319]

80. Gibson L, Lawrence D, Dawson C, et al. Aromatase inhibitors for treatment of advanced breast cancer in postmenopausal women. The Cochrane database of systematic reviews 2009(4):Cd003370. [PubMed: 19821307]

81. Niravath P Aromatase inhibitor-induced arthralgia: a review. Annals of oncology : official journal of the European Society for Medical Oncology 2013;24(6):1443–9. [PubMed: 23471104]

82. Shah DJ, Hirpara R, Poelman CL, et al. Impact of Radiation Therapy on Scleroderma and Cancer Outcomes in Scleroderma Patients With Breast Cancer. Arthritis care & research 2018;70(10):1517–24. [PubMed: 29316366]
83. Rosenberg SA. IL-2: the first effective immunotherapy for human cancer. Journal of immunology (Baltimore, Md : 1950) 2014;192(12):5451–8.
84. Haslam A, Prasad V. Estimation of the Percentage of US Patients With Cancer Who Are Eligible for and Respond to Checkpoint Inhibitor Immunotherapy Drugs. JAMA network open 2019;2(5):e192535. [PubMed: 31050774]
85. Pardoll DM. The blockade of immune checkpoints in cancer immunotherapy. Nature reviews Cancer 2012;12(4):252–64. [PubMed: 22437870]
86. Postow MA, Sidlow R, Hellmann MD. Immune-Related Adverse Events Associated with Immune Checkpoint Blockade. The New England journal of medicine 2018;378(2):158–68. [PubMed: 29320654]
87. Khoja L, Day D, Wei-Wu Chen T, et al. Tumour- and class-specific patterns of immune-related adverse events of immune checkpoint inhibitors: a systematic review. Annals of oncology : official journal of the European Society for Medical Oncology 2017;28(10):2377–85. [PubMed: 28945858]
88. Cappelli LC, Brahmer JR, Forde PM, et al. Clinical presentation of immune checkpoint inhibitor-induced inflammatory arthritis differs by immunotherapy regimen. Submitted for Publication to Seminars in Arthritis and Rheumatism 2018.
89. Cappelli LC, Gutierrez AK, Baer AN, et al. Inflammatory arthritis and sicca syndrome induced by nivolumab and ipilimumab. Annals of the rheumatic diseases 2017;76(1):43–50. [PubMed: 27307501]
90. Chan MM, Kefford RF, Carlino M, et al. Arthritis and tenosynovitis associated with the anti-PD1 antibody pembrolizumab in metastatic melanoma. Journal of immunotherapy (Hagerstown, Md : 1997) 2015;38(1):37–9.
91. Kostine M, Rouxel L, Barnetche T, et al. Rheumatic disorders associated with immune checkpoint inhibitors in patients with cancer-clinical aspects and relationship with tumour response: a single-centre prospective cohort study. Annals of the rheumatic diseases 2018;77(3):393–98. [PubMed: 29146737]
92. Leipe J, Christ LA, Arnoldi AP, et al. Characteristics and treatment of new-onset arthritis after checkpoint inhibitor therapy. RMD open 2018;4(2):e000714. [PubMed: 30167328]
93. Mooradian MJ, Nasrallah M, Gainor JF, et al. Musculoskeletal rheumatic complications of immune checkpoint inhibitor therapy: A single center experience. Seminars in arthritis and rheumatism 2018.
94. Smith MH, Bass AR. Arthritis after cancer immunotherapy: symptom duration and treatment response. Arthritis care & research 2017.
95. Warner BM, Baer AN, Lipson EJ, et al. Sicca Syndrome Associated with Immune Checkpoint Inhibitor Therapy. The oncologist 2019;24(9):1259–69. [PubMed: 30996010]
96. Ramos-Casals M, Maria A, Suarez-Almazor ME, et al. Sicca/Sjogren's syndrome triggered by PD-1/PD-L1 checkpoint inhibitors. Data from the International ImmunoCancer Registry (ICIR). Clinical and experimental rheumatology 2019;37 Suppl 118(3):114–22.
97. Calabrese C, Kirchner E, Kontzias K, et al. Rheumatic immune-related adverse events of checkpoint therapy for cancer: case series of a new nosological entity. RMD open 2017;3(1):e000412. [PubMed: 28405474]
98. Belkhir R, Burel SL, Dunogeant L, et al. Rheumatoid arthritis and polymyalgia rheumatica occurring after immune checkpoint inhibitor treatment. Annals of the rheumatic diseases 2017;76(10):1747–50. [PubMed: 28600350]
99. Calabrese C, Cappelli LC, Kostine M, et al. Polymyalgia rheumatica-like syndrome from checkpoint inhibitor therapy: case series and systematic review of the literature. RMD open 2019;5(1):e000906. [PubMed: 31168414]
100. Goldstein BL, Gedmintas L, Todd DJ. Drug-associated polymyalgia rheumatica/giant cell arteritis occurring in two patients after treatment with ipilimumab, an antagonist of ctla-4. Arthritis & rheumatology (Hoboken, NJ) 2014;66(3):768–9.

101. Micaily I, Chernoff M. An unknown reaction to pembrolizumab: giant cell arteritis. Annals of oncology : official journal of the European Society for Medical Oncology 2017;28(10):2621–22. [PubMed: 28633343]
102. Kimura T, Fukushima S, Miyashita A, et al. Myasthenic crisis and polymyositis induced by one dose of nivolumab. Cancer science 2016;107(7):1055–8. [PubMed: 27420474]
103. Kosche C, Stout M, Sosman J, et al. Dermatomyositis in a patient undergoing nivolumab therapy for metastatic melanoma: a case report and review of the literature. Melanoma research 2019.
104. Liewluck T, Kao JC, Mauermann ML. PD-1 Inhibitor-associated Myopathies: Emerging Immune-mediated Myopathies. Journal of immunotherapy (Hagerstown, Md : 1997) 2017.
105. Shah M, Tayar JH, Abdel-Wahab N, et al. Myositis as an adverse event of immune checkpoint blockade for cancer therapy. Seminars in arthritis and rheumatism 2018.
106. Sheik Ali S, Goddard AL, Luke JJ, et al. Drug-associated dermatomyositis following ipilimumab therapy: a novel immune-mediated adverse event associated with cytotoxic T-lymphocyte antigen 4 blockade. JAMA dermatology 2015;151(2):195–9. [PubMed: 25321335]
107. Barbosa NS, Wetter DA, Wieland CN, et al. Scleroderma Induced by Pembrolizumab: A Case Series. Mayo Clinic proceedings 2017;92(7):1158–63. [PubMed: 28599746]
108. Cho M, Nonomura Y, Kaku Y, et al. Scleroderma-like syndrome associated with nivolumab treatment in malignant melanoma. The Journal of dermatology 2019;46(1):e43–e44. [PubMed: 29863795]
109. Heo MH, Kim HK, Lee H, et al. Antineutrophil Cytoplasmic Antibody-Associated Rapid Progressive Glomerulonephritis after Pembrolizumab Treatment in Thymic Epithelial Tumor: A Case Report. Journal of thoracic oncology : official publication of the International Association for the Study of Lung Cancer 2017;12(8):e103–e05.
110. Dubey D, David WS, Amato AA, et al. Varied phenotypes and management of immune checkpoint inhibitor-associated neuropathies. Neurology 2019;93(11):e1093–e103. [PubMed: 31405908]
111. Loricera J, Hernandez JL, Garcia-Castano A, et al. Subclinical aortitis after starting nivolumab in a patient with metastatic melanoma. A case of drug-associated aortitis? Clinical and experimental rheumatology 2018;36 Suppl 111(2):171.
112. Khoja L, Maurice C, Chappell M, et al. Eosinophilic fasciitis and acute encephalopathy toxicity from pembrolizumab treatment of a patient with metastatic melanoma. Cancer immunology research 2016.
113. Liu RC, Sebaratnam DF, Jackett L, et al. Subacute cutaneous lupus erythematosus induced by nivolumab. The Australasian journal of dermatology 2018;59(2):e152–e54. [PubMed: 28726325]
114. Michot JM, Fusellier M, Champiat S, et al. Drug-induced lupus erythematosus following immunotherapy with anti-programmed death-(ligand) 1. Annals of the rheumatic diseases 2018.
115. Fadel F, El Karoui K, Knebelmann B. Anti-CTLA4 antibody-induced lupus nephritis. The New England journal of medicine 2009;361(2):211–2.
116. Braaten TJ, Brahmer JR, Forde PM, et al. Immune checkpoint inhibitor-induced inflammatory arthritis persists after immunotherapy cessation. Annals of the rheumatic diseases 2019.
117. Horvat TZ, Adel NG, Dang TO, et al. Immune-Related Adverse Events, Need for Systemic Immunosuppression, and Effects on Survival and Time to Treatment Failure in Patients With Melanoma Treated With Ipilimumab at Memorial Sloan Kettering Cancer Center. Journal of clinical oncology : official journal of the American Society of Clinical Oncology 2015;33(28):3193–8. [PubMed: 26282644]
118. Weber JS, Hodi FS, Wolchok JD, et al. Safety Profile of Nivolumab Monotherapy: A Pooled Analysis of Patients With Advanced Melanoma. Journal of clinical oncology : official journal of the American Society of Clinical Oncology 2017;35(7):785–92. [PubMed: 28068177]
119. Judd J, Zibelman M, Handorf E, et al. Immune-Related Adverse Events as a Biomarker in Non-Melanoma Patients Treated with Programmed Cell Death 1 Inhibitors. The oncologist 2017;22(10):1232–37. [PubMed: 28652280]
120. Rogado J, Sanchez-Torres JM, Romero-Laorden N, et al. Immune-related adverse events predict the therapeutic efficacy of anti-PD-1 antibodies in cancer patients. European journal of cancer (Oxford, England : 1990) 2019;109:21–27.

121. Arbour KC, Mezquita L, Long N, et al. Impact of Baseline Steroids on Efficacy of Programmed Cell Death-1 and Programmed Death-Ligand 1 Blockade in Patients With Non-Small-Cell Lung Cancer. Journal of clinical oncology : official journal of the American Society of Clinical Oncology 2018;36(28):2872–78. [PubMed: 30125216]

122. Abdel-Wahab N, Shah M, Lopez-Olivo MA, et al. Use of Immune Checkpoint Inhibitors in the Treatment of Patients With Cancer and Preexisting Autoimmune Disease: A Systematic Review. Annals of internal medicine 2018;168(2):121–30. [PubMed: 29297009]

123. ClinicalTrials.gov. Nivolumab in Treating Patients With Autoimmune Disorders and Advanced, Metastatic, or Unresectable Cancer 2019 [Available from: https://clinicaltrials.gov/ct2/show/NCT03816345?intr=nivolumab&titles=NIVO+AIM&draw=2&rank=1.

Practice Points (box):

- The autoimmune rheumatic diseases are associated with a diverse array of malignancies. It is important for clinicians to understand which malignancies are increased in disease groups and at what point in time in the disease course. Cancer risk and type may vary by disease-specific risk factors such as distinct autoantibodies.
- Though very few prospective malignancy screening trials have been reported in the rheumatic diseases, certain additional testing beyond age and sex appropriate cancer screening can be considered in high risk patients.
- Immune checkpoint inhibitor therapy for cancer can cause a variety of inflammatory syndromes, some of which are similar to traditional rheumatic diseases. There is a limited, but expanding evidence based guidance for treating rheumatic immune related adverse events. Treatment decisions should be made in conjunction with the patient's oncologist, factoring in the risk of cancer progression versus the impact of the immune related adverse event.

Research Agenda (box):

- Careful study of patients who have a close temporal relationship between cancer diagnosis and rheumatic disease onset may provide insight into the link between anti-tumor immunity and development of autoimmunity in the rheumatic diseases.
- Prospective studies are needed to define the optimal approach to cancer screening in high risk rheumatic disease groups (e.g. dermatomyositis patients with NXP-2 or TIF1gamma autoantibodies or scleroderma patients with anti-RNA polymerase III or RNPC3).
- Large scale epidemiologic studies can help determine the safest medications for rheumatic disease in those with previous malignancies.
- Clinical trials to evaluate the most efficacious treatments for rheumatic irAEs that do not impair tumor response to immune checkpoint inhibitors should be performed.

Table 1:

Potential mechanisms linking cancer and the autoimmune rheumatic diseases (Reproduced with permission)[32]

Proposed mechanism	Example(s)
Cancer secondary to rheumatic disease	
Chronic inflammation and damage from rheumatic disease	• Sjogren's: disease activity, severity, duration predictive of non-Hodgkin's lymphoma risk • RA: elevated ESR and CRP associated with increased cancer risk; longer duration corticosteroid therapy associated with lower lymphoma risk • Scleroderma: pulmonary fibrosis associated with lung cancer
Cytotoxic or biologic therapies	• Cyclophosphamide: higher cumulative doses associated with increased risk of lymphoproliferative and bladder cancers • Mycophenolate: Possible increase in non-melanoma skin cancer and Central Nervous System lymphoma • TNF inhibitors: increased risk of non-melanoma and possibly melanoma skin cancer
Inability to clear oncogenic infections	SLE: risk higher for virus-associated cancers (e.g. cervical, vaginal/vulvar, anal cancers associated with HPV)
Rheumatic disease secondary to cancer	
Cancer-induced autoimmunity	• Scleroderma: increased risk of cancer at disease onset among patients with RNA polymerase III autoantibodies; genetic abnormalities of *POLR3A* in cancers associated with mutation-specific T cell immune responses and cross-reactive autoantibodies • Dermatomyositis: striking clustering of cancer diagnosis with disease onset; increased risk of CAM in patients with unique autoantibodies (NXP-2, TIF-1 gamma); clinical improvement in DM with cancer therapy
Immunotherapy or chemotherapy	• IL-2 therapy or immune checkpoint inhibitors: inflammatory arthritis and other autoimmune phenomena have been reported • Bleomycin and gemcitabine: associated with skin sclerosis, development of exacerbation of Raynaud's and ischemic digits
Radiation therapy	Localized scleroderma or fibrosis may develop in radiation port
Shared etiology	
Common inciting exposure	Silica, solvents, organic chemicals, pesticides, smoking, infections, hormonal state
Shared genetic susceptibility	Increased risks of Hodgkin's lymphoma in patients with a personal or family history of multiple autoimmune conditions

RA: rheumatoid arthritis, ESR: erythrocyte sedimentation rate, CRP: C-reactive protein, CAM: cancer-associated myositis, SLE: systemic lupus erythematosus, HPV: human papilloma virus, TNF: tumor necrosis factor, IL-2: interleukin-2

Table 2:

Risk stratifying cancer risk for individual rheumatic diseases

Disease	Factors Associated with Increased Cancer risk	Suggestions for screening, monitoring (in addition to routine age and sex appropriate cancer screening for all patients)
Myositis	Autoantibodies: anti-TIF1gamma, anti-NXP-2	Consider chest/abdomen/pelvis CT at time of diagnosis
	Recent diagnosis (highest risk within 3–5 years)	For women, pelvic ultrasound can be used, particularly in anti-TIF1gamma positive individuals
Rheumatoid arthritis	High levels of disease activity Smoking	Consider chest CT in patients with extensive smoking history Monitoring CBC with differential may be helpful given hematologic malignancy risk, consider checking LDH level if B symptoms
PMR/GCA	Recent diagnosis	Updating all age/sex appropriate cancer screening at the time of new diagnosis should be considered
Scleroderma	Autoantibodies: anti-RNA Pol III, anti-RNPC-3	For those with high risk antibodies and new onset disease, consider chest/abdomen/pelvis CT, mammography, prostate exam +/− PSA at time of diagnosis, ENT examination if globus sensation or unexplained dysphagia
Sjogren's syndrome	High levels of disease activity Presence of cryoglobulins Cytopenias	Monitoring CBC with differential regularly, consider checking LDH if B symptoms develop
	Low complement levels	Test for cryoglobulins and complement levels at time of diagnosis US of parotid glands may identify MALT lymphoma if glands are enlarged or irregular
SLE	Earlier in disease course Immunosuppression (increase risk of cervical intraepithelial neoplasia	Monitoring CBC with differential regularly, consider LDH if B symptoms develop Regular visits with general practitioner or gynecologist for exam given vulvar and cervical cancer risk Yearly Pap smears to monitor for cervical cancer in those on immunosuppressive medications
Vasculitis	Cyclophosphamide cumulative dose	Urinalysis to monitor for microscopic hematuria in those exposed to CYC Monitoring CBC with differential regularly

CBC: complete blood count, LDH: lactate dehydrogenase, CYC: cyclophosphamide, US: ultrasound, MALT: mucosa associated lymphoid tissue, PSA: prostate specific antigen, ENT: ear nose and throat, PMR: polymyalgia rheumatica, GCA: giant cell arteritis, SLE: systemic lupus erythematosus

Table 3:

Treatment of rheumatic immune related adverse events that develop secondary to immune checkpoint inhibitor therapy

irAE	Treatment
Inflammatory arthritis	Mild: standing NSAIDs, intra-articular steroids, low dose prednisone (10–20 mg daily followed by taper)
	Moderate to Severe or Persistent: higher dose prednisone (40 mg daily followed by taper), methotrexate, leflunomide, hydroxychloroquine, TNF-inhibitors, IL-6R inhibitors
Sicca syndrome	Sialogogues
	Dental and Ophthalmologic care (if applicable)
Polymyalgia-like disease	Severe: Prednisone 20–40 mg daily followed by taper[94]
	Prednisone 10–20 mg daily to start, may need higher doses IL-6R inhibitors reported in refractory cases
Giant cell arteritis	High dose oral or IV steroids (40 mg daily-1000 mg IV methylprednisolone pulse)
Myositis	High dose oral or IV steroids (Prednisone 1 mg/kg daily-1000 mg IV methylprednisolone pulse if concern for diaphragmatic involvement) If not responding to Prednisone: IVIG, Plasmapheresis, Rituximab, mycophenolate can be considered