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Rheumatic Diseases and Malignancies

(title)

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SUMMARY

This literature review aims to present different mechanisms of malignancies as a comorbidity in rheumatic diseases and mechanisms of the development of rheumatic syndromes in cancer patients.

Cancer poses a major threat to public health worldwide and is one of the leading causes of death with increasing incidence rates since 1990. Rheumatic diseases are highly prevalent in the general adult population and associated with significant morbidity and therefore pose a major burden for the patients. Due to the bidirectional relationship of both disease entities, there is a high interest in understanding the processes behind these relations.

An electronic search on the online databases PubMed and Google Scholar was performed covering up until March 2022. The time limit was set for papers, which were published not later than 2017. The computerized search was complemented with a manual one of the reference lists of the retrieved articles.

Rheumatic diseases and malignancies are related in a bidirectional manner. Malignancies can be either directly or indirectly related to various rheumatic diseases. Paraneoplastic syndromes may also resemble rheumatic diseases. Additionally, Immune checkpoint inhibitors commonly cause immune related adverse effects, which may resemble various rheumatic diseases. Patients with prostate cancer, who are receiving androgen deprivation therapy are at an increased risk for osteoporosis. It is important to conduct more research about the relationship of rheumatic diseases and malignancies as many of the mechanisms are not yet understood.

Keywords: Rheumatic diseases; Malignancies; Disease-modifying anti-rheumatic therapies; Paraneoplastic syndromes; Immune-related adverse effects; Androgen deprivation therapy

INTRODUCTION

Cancer poses a major threat to public health worldwide and is one of the leading causes of death with increasing incidence rates since 1990 despite efforts being made in cancer prevention, screening, treatment and palliation (1). Rheumatic diseases are highly prevalent in the general adult population and associated with significant morbidity and therefore pose a major burden for the patients (2). The relationship between rheumatic diseases and malignancies is complex, because both groups of these diseases are connected in a bidirectional manner (3–5). One side of the associations between rheumatic diseases and malignancies include the increased risk for the development of malignancies in systemic rheumatic diseases. Firstly, malignancy can be caused by mechanisms of autoimmunity in rheumatic diseases. Additionally the immunosuppressive treatment for rheumatic diseases may also pose an increased risk for the development of malignancies (6). The other side include the development of rheumatic syndromes associated with malignancies. Paraneoplastic syndromes, which are caused by various cancers, can occur and may present as rheumatic syndromes. They are caused by tumor-derived mediators and not by the invasion of the tumor into musculoskeletal tissues (3,7). During the therapy of malignancies there may also occur autoimmune side effects, which can present as rheumatic syndromes. With the use of novel immune checkpoint inhibitors in cancer therapy the prognosis for various malignancies like melanoma and lung cancer can be improved significantly (8,9). However, patients who are undergoing the treatment with immune checkpoint inhibitors may suffer from immune related adverse effects, which may also resemble rheumatic syndromes (10). Furthermore chemotherapy in cancer patients may also lead to immune related adverse effects, which can present as musculoskeletal symptoms (3). Due to the complexity of the bidirectional relationship between rheumatic diseases and malignancies this literature review tries to present the connections of both disease groups in a comprehensible manner.

The goal of this literature review is to present different mechanisms of malignancies as a comorbidity in rheumatic diseases and mechanisms of the development of rheumatic syndromes in cancer patients.

The objectives are to review the current literature on the connections between rheumatic diseases and malignancies, which can be grouped in:

- Malignancies caused directly and indirectly by rheumatic diseases and paraneoplastic rheumatic syndromes.

- Rheumatic syndromes, which are associated with immunotherapy used in the therapy of various cancers, and rheumatic diseases, which are associated with androgen deprivation therapy.

LITERATURE SEARCH STRATEGY

An electronic search on the online databases PubMed and Google Scholar was performed covering up until March 2022 by using the keywords “malignancies” combined with “rheumatic diseases”, “sjogren syndrome”, “rheumatoid arthritis”, “scleroderma”, “myositis”, “systemic lupus erythematosus”, “sarcoidosis”, and “disease modifying anti rheumatic drugs” in all possible combinations. Additionally, the keywords “paraneoplastic rheumatic syndromes”, “checkpoint inhibitors AND rheumatic syndromes”, and “androgen deprivation therapy AND rheumatic diseases” were included in the search. The time limit was set for papers, which were published not later than 2017, and only papers published as full articles in English language were included except for one German article. The computerized search was complemented with a manual one of the reference lists of the retrieved articles. Finally, the abstracts of all retrieved articles were assessed in order to identify studies relevant for this literature review. For the management of the references Zotero bibliography managing software was used.

RESULTS

Malignancies caused by rheumatic diseases

Up until now the full mechanisms on how rheumatic diseases can lead to malignancies are still unknown. The rheumatic disease might just be a paraneoplastic syndrome, which is caused by the malignancy itself. This reason alone however seems to be unlikely, because of reports where secondary tumors have developed even after decades. Several factors may be associated with the pathogenesis of secondary malignancies in rheumatic diseases including genes, viruses and sustained B-cell activation (3,11,12). Many studies have shown that the frequency of some specific malignancies is higher in different rheumatic diseases. Especially malignant lymphoproliferative diseases seem to be apparent in a wide range of rheumatic diseases, which might be explained by the chronic B-cell activation in these diseases (3,11,13). One of the most common lymphoproliferative malignancies associated with rheumatic diseases is the non-Hodgkin’s lymphoma (NHL) (14). The complete mechanisms why autoimmune diseases increase the risk for malignancies are very complex and not completely clear yet. However, it is known that cell injury mediated by autoantigen-specific T-cells or antibodies may lead to autoimmunity induced tumorigenesis. There are 3 types of immunities, which play a role in that

manner. Whereas type 1 and type 3 immunity damage host cells, while clearing intracellular pathogens (e.g. Viruses), type 2 immunity is associated with wound healing. It is thought that this mechanism has evolved to repair the collateral damage, which is done by type 1 and type 3 immunity in acute settings. In chronic settings however the type 2 chronic wound repair can lead to abnormal differentiation of cells and ultimately to tumorigenesis (15).

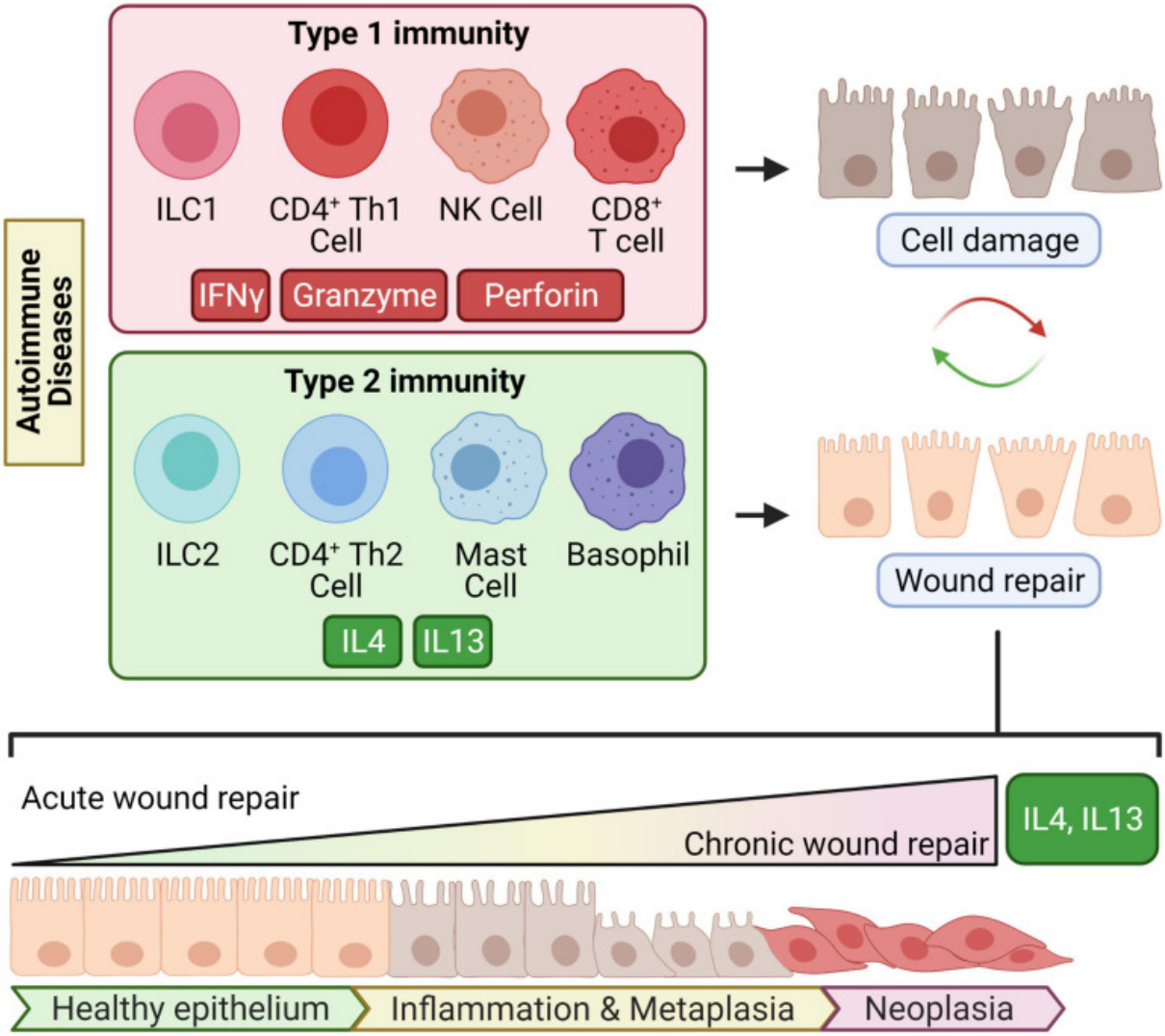

Figure 1. Tumorigenesis caused by type 2 immunity-mediated chronic wound repair.

Adapted from Li CM, Chen Z. Autoimmunity as an Etiological Factor of Cancer: The Transformative Potential of Chronic Type 2 Inflammation. Front Cell Dev Biol. 2021 Jun 21;9:664305.

The innate immune cells which play a role in type 2 immunity are basophils, mast cells and group 2 innate lymphoid cells, which may be activated through alarmins (IL-25, IL-33 and thymic stromal lymphopoietin) following tissue injury. The activated innate cells produce the type 2 cytokines IL-4, IL-5 and IL-13, which triggers the CD4+ T cells differentiation into T helper 2 cells and increases the effector functions of the T helper 2 cells. Ultimately these processes lead to a myofibroblast activation. Chronically activated myofibroblasts may lead to

fibrosis and tissue pathology (16). Another mechanism, which is thought to promote tumor growth, is linked to the sustained B-cell activation in autoimmune diseases. At the inflammation side macrophages and monocytes produce IL-6, which is an activator of the Janus kinase/signal transducer and activator of transcription 3 (JAK/STAT3) signaling pathway. This pathway leads to an upregulated WNT5A gene, which is also frequently upregulated in various malignancies. The STAT3 activation also induces angiogenesis, which is known to be a hallmark of cancer, by upregulation of VEGF-A. The IL-6 cytokine, which is abundant in inflammation sides and may also be increased in tumors, is known to be associated with cancer progression and metastasis (17,18).

Sjogren syndrome and malignancies

The risk of NHL is particularly increased in patients with rheumatoid arthritis, primary Sjogren's syndrome (pSS) and systemic lupus erythematosus (14). In SS patients the occurrence of a B-cell lymphoma within 10 years of SS diagnosis ranges from 5 to 7%. The risk of lymphomas in pSS patients is increased by almost 7-fold compared to the normal population. B-cell lymphomas in pSS usually affect the parotid glands, but may also occur at the stomach, lungs, liver, spleen or orbit. Mortality rates of lymphoma vary in pSS patients between 23% and 33% (19). A meta-analysis from Liang et al. demonstrated that additionally to the increased NHL risk, there is also a significantly increased risk of thyroid cancer in pSS patients (20).

Rheumatoid arthritis and malignancies

A meta-analysis from Simon et al. found that patients with rheumatoid arthritis (RA) have an increased risk of Lymphoma and lung cancer, and a decreased risk of colon and breast cancer. They also suggested that there may be the possibility for an increased risk of malignant melanoma (21). The question, why RA is associated with an increased risk for certain malignancies, is unknown. One theory suggests that this might be explained by shared risk factors. Smoking for example is responsible to cause lung cancer in about 85% of cases and it is also known to increase the risk of RA by 40%. This theory might explain the connection between lung cancer and RA, but it can't explain the relationship between other cancers and RA. The decreased colon cancer risk can be explained by the common use of NSAIDs in the symptomatic treatment of RA. NSAIDs are known to decrease the risk of colon cancer (22).

Scleroderma and malignancies

A meta-analysis from Onishi et al. analyzed 6 population-based cohort studies from Sweden, Scotland, Australia, US, Denmark, and Taiwan with a total number of 6,641 patients with scleroderma. They discovered that the overall cancer risk for scleroderma patients is increased with men having a higher risk than women. Particularly, there was an increased risk of lung, liver, and hematological cancers. In women there was an increased risk of bladder cancer and in men of non-melanomatous skin cancer (23,24). It is not clear, if scleroderma itself causes the increased risk for malignancies or if the cancer induces autoimmunity leading to scleroderma as a paraneoplastic phenomenon. It is also important to note that cytotoxic drugs like cyclophosphamide, which is a common treatment option in scleroderma patients, are associated with an increased risk for malignancies and may influence the statistics (25).

Myositis and malignancies

For the idiopathic inflammatory myopathies' disease group especially patients with Dermatomyositis (DM) show an increased risk for malignancies compared with other subtypes (26). These patients show the highest risk for ovarian, lung, pancreatic, stomach and colorectal cancers and also lymphomas. Polymyositis (PM) patients only show a moderately increased risk for malignancies (27). A meta-analysis from Qiang and colleagues analyzed five population-based studies from Taiwan, Scandinavia, Scotland, and two from Australia regarding the risk of malignancy in inflammatory myositis. In a total of 4538 patients 549 cases of malignancies were diagnosed. They concluded that the overall relative risk of malignancy is higher for DM than for PM patients. Additionally, the risk is higher for men than for women with DM. Contrary to that, in PM patients the cancer risk is higher for women than for men. After the first year of DM diagnosis the risk of cancer is the highest. Regarding the age of DM patients, the risk was especially increased in patients older than 45 (28).

Systemic lupus erythematosus and malignancies

Systemic lupus erythematosus (SLE) is associated with an increased risk of many cancers like Hodgkin's lymphoma, non-Hodgkin's lymphoma, leukemia, multiple myeloma, cervix, vagina/vulva, renal, bladder, esophagus, gastric, hepatobiliary, lung, oropharynx, larynx, non-melanoma skin and thyroid cancers. Interestingly some data suggests that there might be a decreased risk for prostate cancer and melanoma (29). As mentioned earlier, also in the SLE therapy the common use of cyclophosphamide might have an influence on the data, as this drug itself is associated with an increased risk for malignancies. There is also evidence that SLE-

related autoantibodies may increase the risk for cancers by impairing DNA repair, which leads to the accumulation of DNA damage (30).

Sarcoidosis and malignancies

Sarcoidosis is a systemic disease, which is characterized by non-caseating granulomas in various organs and can manifest with rheumatic symptoms. Patients with sarcoidosis are at an increased for malignancies in general. Especially Lymphomas seem to be more prevalent in these patients. Other solid tumors might also be more common, but this needs to be studied more due to conflicting data (31). The increased frequency of malignancies in these rheumatic disease patients leads to the question, if this is caused by a failure of the immune system to target malignant cells. However, contrary to the common expectation that immunosuppressive treatment (e.g. with NSAIDs or steroids) would favor the development of malignancies in patients with autoimmune diseases, it has been shown that this kind of treatment decreases the risk for malignancies in rheumatic patients by suppressing the inflammatory processes, which are linked to cancer initiation and progression (32).

Malignancies associated with the treatment of rheumatic diseases

Malignancies may also be indirectly associated with Rheumatic diseases. Cytotoxic and biologic therapies of various rheumatic diseases are linked to an increased risk of some malignancies (33). However, it poses a difficult task to evaluate, whether the malignancy is caused by the therapeutic agent or by the rheumatic disease itself. Also, the sequential or combined use of the drugs makes it difficult to assess the cancer risk of single drugs (32).

NSAIDs and malignancies

NSAIDs are one of the most common drugs prescribed for the symptomatic treatment of rheumatic diseases, especially for arthritis. These drugs may cause a variety of serious side effects including gastrointestinal, cardiovascular and renal side effects. The current literature has conflicting views, if NSAIDs are associated with an increased or decreased risk of cancers. Most of these studies suggest that this group of drugs exhibits cancer-protective effects, which may be explained by the anti-inflammatory action of NSAIDs due to the relation between chronic inflammation and carcinogenesis. Some other studies found that NSAIDs may be associated with an increased risk for some malignancies (34,35). However, the underlying mechanisms in these studies were less clear (36). A meta-analysis from Harewood et al. suggests that NSAIDs is associated with protective effects for proximal colon cancer (37).

Glucocorticoids and malignancies

Additionally to NSAIDS, glucocorticoids are also very widely used for the treatment of rheumatic diseases due to their strong anti-inflammatory properties and effective reduction in burdensome rheumatic symptoms. A nationwide case-control study from Sweden assessed the lymphoma risk in Polymyalgia rheumatica and giant cell arteritis patients treated with glucocorticoids. They found that there is no increase in lymphoma risk in selected patients, who take moderate to high daily doses of steroids. Instead, the lymphoma risk was moderately reduced (38).

Cytotoxic medications for rheumatic diseases and malignancies

Cyclophosphamide is a cytotoxic agent, which is commonly used for the treatment of various malignancies such as breast cancer and multiple myeloma. However, it may also be used in many rheumatic diseases like rheumatoid arthritis, dermatomyositis, systemic sclerosis, systemic lupus erythematosus and systemic vasculitis. This drug increases the risk for cancers when used as a long-term treatment (39). Especially the risk for bladder cancer is increased. This is due to the toxic metabolite acrolein, which is excreted by the kidneys and concentrated into the urine. Additionally, secondary acute leukemia and skin cancer are related to the long-term treatment with cyclophosphamide (40).

Mycophenolate is another disease modifying anti rheumatic drug with a inhibitory action on the proliferation of T-Cells and B-Cells (41), which is used for the treatment of rheumatic diseases and is associated with an increased risk for malignancies. However, there is still lacking evidence, if mycophenolate alone increases the risk for some cancers as most studies only described patients with multiple concomitant immunosuppressive therapies. Some studies suggest that mycophenolate is associated with an increased risk for non-melanoma skin cancer and CNS lymphoma (33).

Additionally, Methotrexate is widely used as a first line agent for the treatment of rheumatoid arthritis due to its high efficacy. It has a cytostatic mechanism of action by inhibiting DNA synthesis, repair and cellular replication. Despite its high efficacy and relatively low toxicity methotrexate still may cause some serious side effects including cancer. Mainly it is associated with an increased risk for lymphomas and pseudo lymphomas. It is not completely clear yet, if Methotrexate alone increases the risk for malignancies or if the risk is related to the pathogenesis of rheumatoid arthritis contributing to the development of cancer. However, the

withdrawal of methotrexate in cancer patients with rheumatoid arthritis showed sometimes regression of these tumors (42).

Biologicals for rheumatic diseases and malignancies

The treatment with TNF inhibitors in rheumatoid arthritis patients was thought to promote the growth of cancers. However, a recent observational, nationwide cohort study from Sweden concluded that the overall risk for cancers, excluding skin cancers, in rheumatoid arthritis patients treated with TNF inhibitors is not increased compared to rheumatoid arthritis patients treated with other therapy regimens (43).

Rheumatic syndromes associated with malignancies

Paraneoplastic syndromes

The increasing life expectancy of humans, and the growing number of patients with cancer will likely cause an increase in the incidence of paraneoplastic syndromes. Paraneoplastic syndromes are caused by malignancies, but they are not related to direct tumor invasion or its metastases. They are related to the tumor secretion of functional peptides and hormones or to an immune cross-reactivity between tumor and healthy host tissue (44). The paraneoplastic syndrome may even be diagnosed up to 2 years before the malignancy itself, which may be an important hint for an underlying neoplasia. However, sometimes it may be difficult to attribute the paraneoplastic syndrome to the malignancy. The definite evidence for the paraneoplastic etiology is the disappearance of the condition after the curative treatment of the malignancy (7). Paraneoplastic syndromes can reflect many different diseases, which occur outside of malignancies, including various rheumatic syndromes (44). Rheumatic paraneoplastic syndromes include arthritides, autoimmune connective tissue diseases, vascultitides, skin and muscles diseases, and metabolic diseases (11). Paraneoplastic arthritides are a group of rare arthropathies, which are associated to a distant malignancy and are caused by immune-mediated mechanisms. These syndromes are characterized by joint pain, swelling and stiffness, and may mimic other rheumatic diseases such as rheumatoid arthritis (7).

Paraneoplastic arthritis is one disease of this group and typically presents as an asymmetric oligoarthritis with a rapid onset, but polyarthritis and monoarthritis are also possible clinical presentations. The average age at disease onset is 50 years and therefore higher than the age in rheumatoid arthritis. Most patients show an absence of elevated rheumatoid factor titers and cyclic citrullinated peptide antibodies. Contrary to rheumatoid arthritis, the radiographs in paraneoplastic polyarthritis patients show an absence of joint erosions and joint space

narrowing. One third of patients have an underlying hematological malignancy. Cases of adenocarcinomas of lungs and breast cancer are also known to cause this syndrome (7,45). The pathogenesis remains unknown up today. However, in one case of renal carcinoma the same T-cell clone could be found as an infiltration in the tumor tissue and in the synovium (46). Only the curative treatment of the underlying malignancy will improve the symptoms. NSAIDs or glucocorticoids are associated only with minimal symptom improvement (7).

Hypertrophic osteoarthropathy (HOA) is another rheumatic paraneoplastic syndrome and is associated with malignant and non-malignant diseases of the lungs. Especially the bronchial adenocarcinoma is associated with the occurrence of HOA. Clinical signs of HOA include tibial and femoral bone pain due to periosteal osseous proliferations and periostitis. Additionally, arthralgia and mild arthritis may affect the adjacent joints. Also clubbing of the fingers and/or toes are characteristic findings in HOA. More seldomly encountered signs of HOA are acanthosis palmaris and hyperkeratotic accentuation of dermatoglyphic lines. It is hypothesized that bone formation and clubbing is promoted by the platelet-derived growth factor (PDGF), which is released by megakaryocytes that have bypassed the lung capillaries through pathologic shunts. These shunts may be the consequence of various lung diseases. Vascular endothelial growth factor (VEGF) seems to have an even greater impact on the pathogenesis of HOA and synergizes with PDGF. Tumor cells increasingly secrete VEGF, which is a key cytokine in the pathogenesis of HOA by the promotion of the proliferative periostitis. The main goal in the treatment of HOA is the complete remission of the underlying malignancy. Besides the treatment of the malignancy, symptoms can usually be controlled effectively by NSAIDs. Also zoledronic acid and octreotide are effective treatment options by the inhibition of VEGF (7,47).

Relapsing seronegative symmetric synovitis with pitting edema (RS3PE) is another rheumatic arthropathy, which may occur not only idiopathically, but also secondarily in colon, lung, gastric, prostate and endometrial cancer, and T-cell lymphoma, leukemia and myelodysplasia as a paraneoplastic syndrome. Clinical signs in secondary RS3PE conclude bilateral nonerosive synovitis of small joints and edema of the hands and feet. It mostly affects elderly males with an average of 71 years of age. The diagnosis is usually made clinically due to the absence of rheumatoid factor and other autoimmune serum markers. VEGF may play a role in the pathogenesis of RS3PE by leading to an increased vascularization and vascular permeability. It is unknown why metalloproteinase 3 levels are elevated in the blood serum of RS3PE patients and if this enzyme plays a role in the pathogenesis of this disease. Usually, RS3PE patients respond well to the administration of steroids. However, in patients with secondary RS3PE the

glucocorticoid response is diminished, which should be a hint for an underlying malignancy (7,11,48).

Palmar fasciitis with polyarthritis (PFPA) is a rare disease and also belongs to the group of paraneoplastic arthropathies. It mostly affects woman due to the association with ovarian, breast and other female urogenital cancers. Additionally, it is associated with gastrointestinal, lung and hematological malignancies. The typical clinical picture of PFPA is symmetrical painful swelling of the hands with flexion contractures and synovitis of the metacarpophalangeal and proximal interphalangeal joints leading to the characteristic “woody hands” phenomenon. The pathogenesis of PFPA remains unknown, but the connective tissue growth factor may play a role. Only the complete resection of the primary tumor can cure the paraneoplastic PFPA. However, PFPA is mostly an irreversible condition, because the diagnosis of this syndrome is mostly made in patients with advanced cancer and the response to glucocorticoids, NSAIDs or immunosuppressives is limited (7,49).

A very rare syndrome of the paraneoplastic arthropathies is the pancreatic panniculitis with polyarthritis (PPP) syndrome, which is most commonly associated with acinar cell carcinoma of the pancreas. The clinical signs are symmetrical polyarthritis of the knee, ankle, elbow, metatarsal and metacarpal joints, but also monoarthritis of large joints has been reported. The panniculitis presents with erythematous painful skin nodules in the pretibial region, ankles and knees. It is thought that the symptoms are caused by the release of pancreatic enzymes, which lead to a fat necrosis of periarticular tissue and subcutaneous adipose tissue. Additionally, the release of free fatty acids through lipolysis of periarticular fat tissue into the joint spaces may cause the arthritis-like symptoms. The main treatment goal in the PPP syndrome is the surgical resection of the pancreatic tumor in order to get a symptom relief. Symptomatic treatment with NSAIDs and glucocorticoids is controversial (45,50).

Apart from rheumatic arthropathies, paraneoplastic syndromes may also resemble various forms of myositis. Cancer-associated myositis (CAM) is defined as the occurrence of a malignancy within 3 years of the myositis diagnosis. Dermatomyositis has the highest association with malignancies, whereas the association with cancer is much weaker for polymyositis and inclusion-bodies myositis. Patients with dermatomyositis most often have ovarian, pancreatic, stomach and colorectal cancers. Polymyositis is associated with lung and bladder cancers, and NHL can appear in both forms of myositis. Generally, CAM patients tend to be older than patients with idiopathic forms of myositis. CAM also presents with a more severe muscular and cutaneous involvement, but less commonly with interstitial lung disease

(47). There are several cancer-associated autoantibodies, which may be involved in the pathogenesis of CAM including autoantibodies against transcriptional intermediary factor 1-gamma (TIF1-γ), nuclear matrix protein-2 (NXP-2), 3-hydroxy-3-methylglutaryl-coenzyme A reductase (HMGCR), and small ubiquitin-like modifier 1 activating enzyme (SAE). One of the known mechanisms is that TIF1-γ leads to a downregulation of the tumor suppressor gene p53 causing a reduced apoptosis of tumor cells. Anti-HMGCR autoantibodies caused in-vitro atrophy of myotubes and myofibers (7,51). Glucocorticoids usually alleviate the CAM symptoms significantly. The curative treatment of the underlying malignancy leads to a symptom relief in only half of the patients with CAM. The CAM might recur after the successful treatment of the malignancy even without a tumor relapse (47).

Paraneoplastic vasculitides are very rare, with cutaneous leukocytoclastic vasculitis being the most frequent type. Clinically this syndrome presents with palpable purpura mainly on the lower extremities and ankles with necrotizing inflammation around dermal blood vessels. More often paraneoplastic vasculitis is caused by hematological malignancies than solid tumors. Cutaneous leukocytoclastic vasculitis is associated with myelodysplastic syndrome, lymphomas and hairy cell leukemia. Regarding the pathogenesis and treatment is not much known (7,52). There is one case of a 57 year old man with leukocytoclastic vasculitis and acute myeloblastic leukemia who responded well to the administration of potent topical steroids (52).

Tumor-induced osteomalacia (TIO) is a rare rheumatic paraneoplastic syndrome, which belongs to the metabolic subgroup of paraneoplastic diseases. TIO is associated with the very rare group of phosphaturic mesenchymal tumors (PMTs), which are small tumors that can be located anywhere in the body's soft tissue or bone. Sino-nasal hemangiopericytomas and osteosarcomas are also possible causes of TIO. Due to unspecific symptoms in TIO, the diagnosis after the onset of symptoms is often delayed ranging from 2.5 to 28 years. Clinical signs include bone fractures, muscle weakness, height loss, hypophosphatemia, hyperphosphaturia, and normal or low levels of 1,25-dihydroxycholecalciferol. The pathogenesis of TIO is characterized by the increased secretion of endocrine fibroblast growth factor 23 (FGF23) by the tumor cells, which binds to cells in the proximal tubule of the kidneys and decreases the renal tubular phosphate reabsorption. If the underlying tumor can be resected, the prognosis is excellent with a rapid disappearance of symptoms. The tumor removal was successful, when the FGF23 serum concentration return to normal ranges. Otherwise a supplementation with phosphate and 1,25-dihydroxycholecalciferol is needed (47,53).

Checkpoint inhibitors and rheumatic syndromes

Immune checkpoint inhibitors (ICI) have been one of the greatest breakthroughs in cancer therapy during the last decade. These drugs belong to a class of cancer immunotherapies, which target specific immune checkpoints on immune cells or cancer cells. Under physiologic circumstances immune checkpoints serve the purpose to protect the body from immune responses, which may cause potential damage. However, cancer cells are able to utilize these immune checkpoints in order to evade the immune system by downregulating T-cell responses. Therefore, by blocking these immune checkpoints with immune checkpoint inhibitors it is possible to induce an anti-tumor response (54). The cytotoxic T-Lymphocyte-associated antigen 4 (CTLA-4) and programmed death protein 1 (PD-1) immune checkpoint pathways are the two main pathways, which play a role in the anti-tumor immunity. Tumor antigens are presented by the major histocompatibility complex (MHC) of the antigen presenting cells to the T-cell receptors (TCR) of the T-cells. Just the presentation of tumor antigens to T-cells via antigen presenting cells would not be sufficient in order to activate a T-cell mediated anti-tumor response.

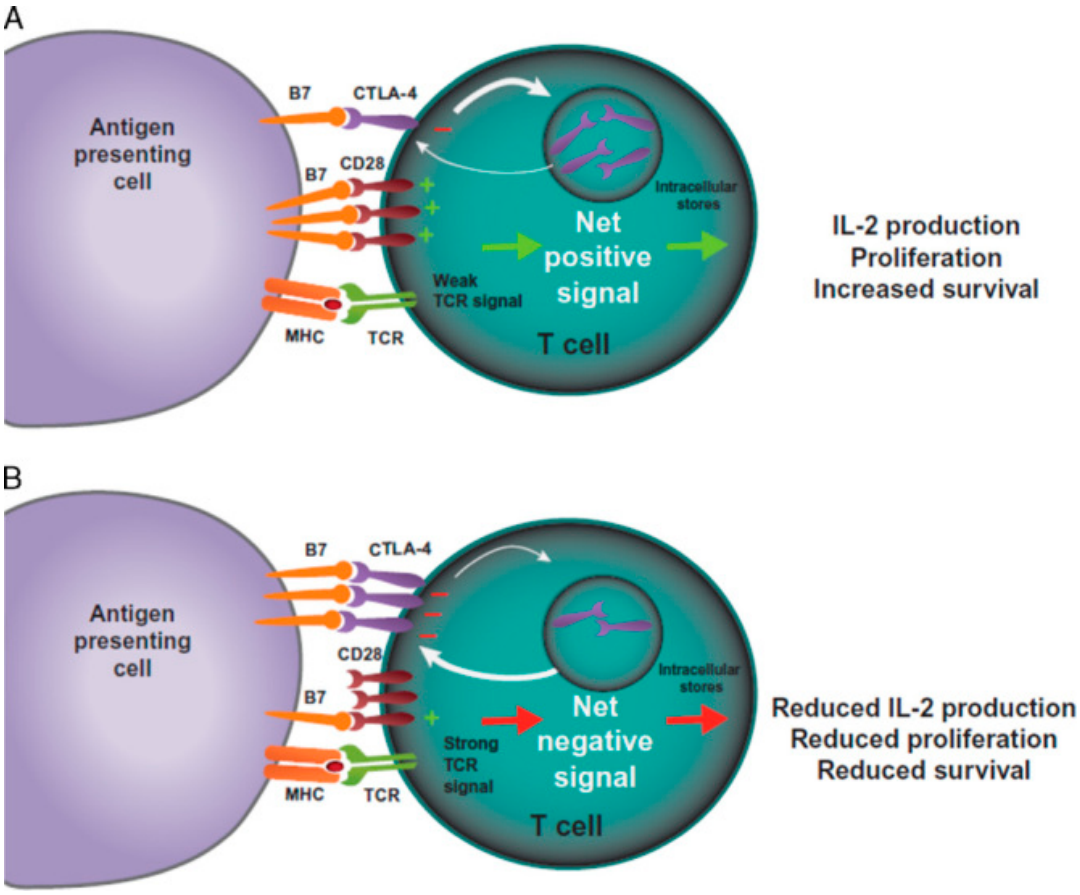

Figure 2. (A) Dominant costimulation of T-cells. (B) Dominant coinhibition of T-cells.

Adapted from Buchbinder EI, Desai A. CTLA-4 and PD-1 Pathways: Similarities, Differences, and Implications of Their Inhibition. Am J Clin Oncol. 2016 Feb;39(1):98–106.

Therefore, a costimulation via the B7 and the CD28 molecule binding is needed, which then leads to an increased IL-2 production and increased T-cell proliferation and survival. In the case of a dominant coinhibition via the B7 and CTLA-4 molecule binding the IL-2 production is reduced, which leads to a decreased T-cell proliferation and survival (Fig. 2) (3,55). If the T-cells got activated by the antigen presenting cells, they can migrate as tumor infiltrating lymphocytes (TIL) to tumor cells and can undergo a TCR-MHC binding in order to induce apoptosis in tumor cells. However, tumor cells often express the programmed death protein ligand 1 (PD-L1), which can bind to the PD-1 molecule expressed on TIL. This coinhibitory PD-1:PD-L1 binding induces apoptosis of TILs and suppresses cytokine secretion and T-cell proliferation (Fig. 3) (3,55,56).

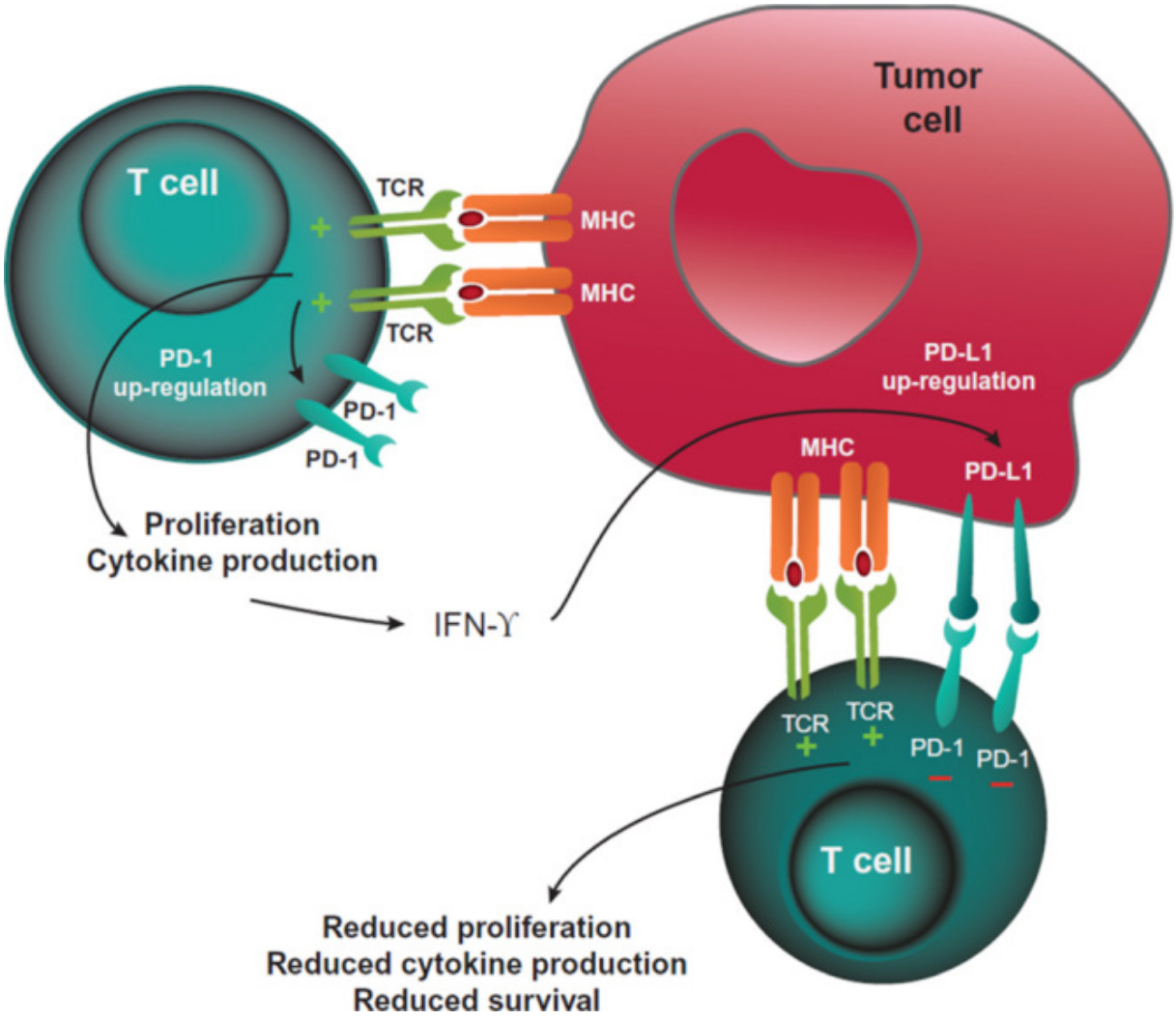

Figure 3. PD-1-mediated inhibition of T-cells.

Adapted from Buchbinder EI, Desai A. CTLA-4 and PD-1 Pathways: Similarities, Differences, and Implications of Their Inhibition. Am J Clin Oncol. 2016 Feb;39(1):98–106.

These immune checkpoint pathways can be blocked by ICIs. ICIs are monoclonal antibodies, which can bind to the CTLA-4, PD-1 and PD-L1 molecules leading to an induction of an anti-

tumor response (57). The indications of ICIs approved by the FDA include a wide range of malignancies including small cell and non-small cell lung cancer, melanoma, renal cell carcinoma, squamous cell cancer of head and neck, breast cancer, gastric cancer, urothelial cancer, Merkel cell carcinoma, hepatocellular carcinoma, cervical cancer and Hodgkin lymphoma (58). For a subset of cancer patients the therapy with ICIs shows good responses and may even cure advanced and metastatic cancers (59). However, the response rates of ICIs seem to correlate with the occurrence of immune-related adverse events (irAEs). A meta-analysis from Canada discovered that the development of irAEs is connected to increased survival rates in these patients, which might be explained by similar antigens presented on tumor cells and on healthy tissues (60). Szekanecz et al. were the first ones to discover in 1995 that tumor-associated antigens are not only expressed by tumor cells but could also be expressed by inflammatory leukocytes. They found carcinoembryonic antigens on synovial macrophages in Rheumatoid arthritis patients (61). Additionally, due to the increased T-cell activation during the therapy with ICIs, B-cells are getting activated by the T-cells resulting in an autoantibody production. For example, patients who were receiving ICIs developed arthritis with increased levels of rheumatoid factor and anti-cyclic citrullinated peptide (54). The irAEs can occur throughout the whole body and can affect any organ system. Gastrointestinal, endocrine, skin and liver involvements are the most frequent irAEs (62). It is important to note that the irAEs are usually more frequent, when a combination therapy of CTLA-4 and PD-1 inhibitors are given than just a monotherapy alone with either of these regimens (8). Risk factors for developing irAEs are preexisting autoantibodies and preexisting autoimmune diseases. In a medical record analysis from Japan 137 patients with an ICI monotherapy were analyzed. It was shown that patients with preexisting autoantibodies were more likely to develop irAEs (63). A systematic review from Abdel-Wahab et al. analyzed 123 cases of patients who had preexisting autoimmune diseases that had been treated with ICIs. According to this review 91 patients (75%) experienced an irAE and 61 patients (50%) had an exacerbation of their preexisting autoimmune disease (64). This review put the focus on the rheumatic irAEs. According to a systematic literature review from the US arthralgia (up to 40%) and myalgia are the most common rheumatic irAEs due to ICIs. Rheumatic irAEs, which they reported to occur after the administration of ICIs, are inflammatory arthritis, inflammatory myopathy, vasculitis, and lupus nephropathy (65). Less commonly seen rheumatic irAEs are sarcoidosis, vasculitis, systemic lupus erythematosus, antiphospholipid syndrome, scleroderma-like syndromes, hemophagocytic lymphohistocytosis and bone abnormalities (66). Inflammatory arthritis occurs in patients treated with ICIs from 1 – 7% and may persist even after the discontinuation

of ICI therapy (67,68). Various phenotypes of inflammatory arthritis are known to occur after the treatment with ICIs including small joint predominant polyarthritis, large joint oligoarthritis (in lower extremities usually), tenosynovitis, psoriatic-type arthritis and remitting seronegative symmetrical synovitis with pitting edema (67). In around 50% of cases the shoulder, metacarpophalangeal and proximal interphalangeal joints of the hands are affected, followed by knees and wrists (40%) (69). Rheumatoid factor and anti-citrullinated protein antibodies are usually not elevated in these patients. Inflammatory markers are increased in two thirds of the patients with arthritis (67,69). According to the common terminology criteria for adverse events (CTCAE) inflammatory arthritis can be graded from grade 1 to 3 according to the severity of the irAE. The management of these irAEs consists of corticosteroids and NSAIDs in conjunction with DMARDs depending on the severity grade. If the inflammatory arthritis is at grade 3 the ICI treatment should be discontinued (70). Myositis is another irAE, which doesn't occur as frequently as arthritis, but it is a potentially life-threatening adverse event. It usually presents with Myalgia and proximal muscle weakness. Some patients present with oculomotor and bulbar symptoms. Dyspnea should be a hint for myocarditis, which is a serious complication (69). In most of the myositis cases an elevation of the Creatine Kinase levels can be noted. If a myositis is suspected the ICI therapy should be discontinued and steroid treatment should be initiated (71). Polymyalgia-rheumatica-like (PMR-like) syndrome is characterized by bilateral shoulder pain, morning stiffness, restricted movement in proximal limbs and the absence of myositis or weakness. There are not many studies about this PMR-like syndrome, and it is difficult to compare it with Polymyalgia rheumatica (PMR) due to missing diagnostic tests. Therefore, a case series was conducted from Calabrese et al., if the PMR-like syndrome applies to the EULAR/ACR criteria from 2012. They analyzed 37 patients from which 28 (75%) fulfilled the criteria, whereas the rest demonstrated some unusual features for PMR (72). PMR-like syndrome with mild symptoms can just be managed with NSAIDs. Otherwise a treatment with moderate doses of steroids would be indicated without discontinuing the ICI therapy (73). Sicca syndrome, which is characterized by xerostomia and xerophthalmia may also occur as a rheumatic irAE. Warner et al. evaluated 20 Patients with new onset or worsening of dry mouth symptoms. In 18 patients there was a new onset and in 2 an exacerbation of sicca syndrome. Most of these patients had no elevation of autoantibodies. 3 patients were ANA positive, with 2 of them being already positive before the ICI treatment. And 2 patients were positive for RF and anti-SSA antibodies, with one of them being positive before. 12 of these patients were treated with steroids with moderate improvement of the symptoms. A complete resolution of the symptoms has not been reported in any of the patients even after the discontinuation of the

ICI therapy (74). In patients with a preexisting rheumatic disease the therapy with ICIs often leads to disease flares, which could generally be managed without discontinuing the ICI treatment (67).

Androgen deprivation therapy and rheumatic diseases

The most common cancer in men is prostate cancer. Despite treatment, many patients with high risk, locally advanced or metastatic prostate cancer die from this disease. Due to the prostate's dependence on Androgens for growth and progression, androgen deprivation therapy (ADT) is a common treatment for prostate cancer (75). Although the prostate tumor cells are directly affected by the ADT, the lack of androgens may also have significant effects on the immune system. Testosterone and dihydrotestosterone have immunosuppressive effects by increasing the proliferation of regulatory T-cells and the production of IL-10 and by decreasing the IFNγ secretion. They also induce a decrease in thymus weight and an increase in prostate weight. Contrary to that, ADT enhances the immune function by increasing naïve T-cell numbers, antigen-specific T-cells and IFNγ production. ADT can be done as a surgical castration or chemically by the administration of medications (76). Surgical castration is done by a bilateral orchiectomy, which would lead to a rapid decrease in testosterone levels. On the other side, medical castration, which is the more frequently chosen therapy option due to its reversibility, mainly consists of a gonadotropin releasing hormone (GnRH) agonist administration resulting in an initial LH and FSH release from the hypothalamus. Due to increased testosterone levels and increased risk for tumor flares after the start of the treatment, a coadministration of an androgen receptor antagonist is recommended for the first 2-4 weeks. After 4-8 weeks the ADT leads to a downregulation of the pituitary gland receptors and ultimately to castration levels of testosterone (77). Additionally, androgens promote longitudinal bone growth and radial bone growth. Patients with advanced prostate cancer who underwent ADT show an accelerated bone degradation and an increased risk for bone fractures (78). A systematic review from Taylor at al. concluded that men who are undergoing ADT are at an increased risk for osteoporosis or loss in bone mineral density compared to men who didn't receive ADT. Osteoporosis is usually not diagnosed, before the treatment duration of 4 years. However, they found that the bone mineral density is already significantly reduced with an ADT treatment duration for less than a year (79).

A large population-based cohort study from Yang et al. demonstrated for the first time the possible relationship between androgen deprivation therapy and rheumatoid arthritis. They found that patients who received any kind of ADT had a 23% increased risk of being diagnosed

with rheumatoid arthritis. Additionally, they found an association between the duration of ADT and risk of rheumatoid arthritis. 1-6 months of ADT duration demonstrated a 19% risk of developing rheumatoid arthritis. For the duration of 7-12 months the risk was at 29% and for more than 13 years the risk was at 33% (80). Another population-based cohort study from Klil-Drori at al. found one year later in 2019 that the risk of developing RA in ADT receiving patients is not increased. They included 32,302 men with a median follow up of 3.3 years. 63 patients were newly diagnosed with RA during the follow-up. The ADT patients' group didn't show an increased risk of RA compared to the non-ADT patients' group (81). Due to this conflicting data further studies are needed to clarify the association between ADT and the risk of RA.

DISCUSSION

There are many mechanisms, which may explain the relationship between rheumatic diseases and malignancies. The increased risk of some cancers seems to be apparent in various rheumatic diseases as it was reported in this review for Sjogren syndrome, rheumatoid arthritis, scleroderma, myositis, systemic lupus erythematosus and sarcoidosis. Even though the exact mechanisms are not clear yet, it seems that these diseases themselves may be accountable for this increased risk. However, it is important to do more research in this field due to other possible mechanisms, which can explain the increased risks. Other mechanisms include shared risk factors (e.g. smoking as a shared risk factor for rheumatoid arthritis and lung cancer), malignancies associated with the treatment of rheumatic diseases (e.g. cyclophosphamide treatment in scleroderma), and possibility of the rheumatic disease being caused by the malignancy as a paraneoplastic syndrome. Additionally, the treatment of rheumatic diseases with disease modifying drugs can be associated with malignancies. Someone might think that the treatment with NSAIDs and steroids would inhibit the immune system in fighting tumor cells, but in reality, there is evidence that the anti-inflammatory actions of these drugs exhibit cancer-protective effects. However, this might not be the case for other disease modifying drugs. Some studies found some significant data, in which the long-term use of cyclophosphamide increases the risk for bladder cancer. For other drugs it is less clear, and more data needs to be collected. On the other side malignancies may cause rheumatic syndromes either directly or indirectly. Directly caused rheumatic syndromes are called rheumatic paraneoplastic syndromes. Due to the increasing life expectancy of humans, the incidence of malignancies in the elderly will increase in the future. Therefore, physicians will encounter paraneoplastic syndromes more often and they need to be aware that these syndromes

might manifest before the cancer itself. A rheumatic syndrome in the elderly should always be a hint for a possible underlying malignancy. This allows an early screening for cancer and may improve the prognosis, if the malignancy is found early. Additionally, paraneoplastic rheumatic syndromes do not respond well to antirheumatic treatments, which should be another hint for the physician. The focus should be put on the curative treatment of the underlying malignancy, because only with the remission of the tumor a relieve of rheumatic symptoms can be achieved. Additionally, malignancies are related to rheumatic diseases with the use of ICIs, which are known to cause rheumatic irEAs. Physicians should be aware that ICIs may cause these irAEs, because there are cases where the side effects can't be controlled with medications and a discontinuation of ICIs are needed. Sometimes the treatment with ICIs is a dilemma for oncologists, because a good ICI effect is linked to more severe irAE. Therefore, it is crucial that these irAEs are monitored and treated early in order to lower the burden for the patients. Another common problem is that many patients may not be aware of side effects like arthritis and do not report them to their physician, because they might think that this is just part of getting older in age. Therefore, the actual number of rheumatic irAEs could be me much higher. A general problem in studying rheumatic irAEs is that it is difficult to compare rheumatic irAEs with the idiopathic forms of rheumatic diseases due to missing diagnostic markers/tests and unusual features of rheumatic irAEs (e.g. in PMR-like syndrome). Finally, androgen deprivation therapy, which is primarily used in the treatment of advanced prostate cancer, is associated with accelerated bone degradation and an increased risk for bone fractures. However, this therapy in general is also associated with chronic stress in men, which ultimately could be a possible cause for osteoporosis (82). Furthermore, due to conflicting data in the most recent studies related to the rheumatoid arthritis risk in ADT receiving patients, it is not clear whether there is an increased risk of RA or not.

CONCLUSION

Rheumatic diseases and malignancies are related in a bidirectional manner. On one hand, malignancies can be directly related to various rheumatic diseases. Mechanisms for this are chronic type 2 immunity wound repair and sustained B-cell activation. Also, genes and viruses may be involved in secondary malignancies. On the other hand, malignancies can be caused indirectly by rheumatic diseases. Cytotoxic and biologic therapies of various rheumatic diseases are linked to an increased risk of malignancies. Paraneoplastic syndromes, which are caused by tumor secretion of functional peptides and hormones or by an immune cross-reactivity between tumor and healthy host tissue, may also resemble rheumatic diseases. Furthermore, with the use

of novel immune checkpoint inhibitors immune related adverse effects commonly occur and may resemble various rheumatic diseases. Rheumatic immune related adverse effects may be associated with T-cell induced autoimmunity and increased autoantibody production. Patients with prostate cancer, who are receiving androgen deprivation therapy are at an increased risk for osteoporosis due to an accelerated bone degradation caused by the lack of androgens. It is important to conduct more research about the relationship of rheumatic diseases and malignancies as many of the mechanisms are not yet understood.

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