Autoimmunity Reviews 19 (2020) 102658

Contents lists available at ScienceDirect

Autoimmunity Reviews

journal homepage: www.elsevier.com/locate/autrev

Eight pillars of oncorheumatology: Crossroads between malignancies and musculoskeletal diseases

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ARTICLE INFO

Keywords:
Oncorheumatology
Musculoskeletal diseases
Tumors
Secondary tumor development
Carcinogenicity
Targeted therapy
Immune-checkpoint inhibition
Sarcomas

ABSTRACT

Oncorheumatology: relationship between malignancies and musculoskeletal diseases: Oncorheumatology is the meeting point of tumor formation and rheumatic musculoskeletal diseases (RMD). Multiple interactions exist between these two medical specialties. One major field is the topic of malignancies associated with rheumatic diseases, while the other topic covers the development of musculoskeletal disease in cancer patients. Within the first group, secondary malignancies may be associated with rheumatic diseases. Mostly sustained inflammation is responsible for transition into cancer. Tumor-associated antigens (TAA) with adhesive properties are present on tumor cells. These molecules may also be expressed by inflammatory leukocytes and soluble TAA levels may be elevated in RMDs. There has been continuous debate with respect to the possible carcinogenicity of conventional and targeted antirheumatic drugs. Very recent data from registries suggest that neither biologics, nor JAK inhibitors increase cancer risk in arthritis patients. The issue of physiotherapy in rheumatic patients with recent or current cancer has also been controversial. Some modalities, primarily exercise, may be safely applied to patients with RMD and cancer. The second large topic includes paraneoplastic syndromes. Musculoskeletal paraneoplasias are triggered by tumor-derived mediators. These syndromes are sometimes slightly different from the classical RMDs. Various chemotherapies may also be associated with autoimmune side effects. Recently, these immune-related complications have also been observed in cancer patients treated with immune-checkpoint inhibitors. Sex hormone-deprivation therapies, such as aromatase inhibitors and anti-androgens are widely used for the treatment of breast and prostate cancer, respectively. These compounds may induce bone loss and lead to osteoporosis. Finally, primary and secondary malignancies of the musculoskeletal system may also interest rheumatologists. In this review, the clinical, practical aspects of these eight pillars of oncorheumatology will be discussed.

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https://doi.org/10.1016/j.autrev.2020.102658
Received 24 March 2020; Accepted 31 March 2020
Available online 14 September 2020

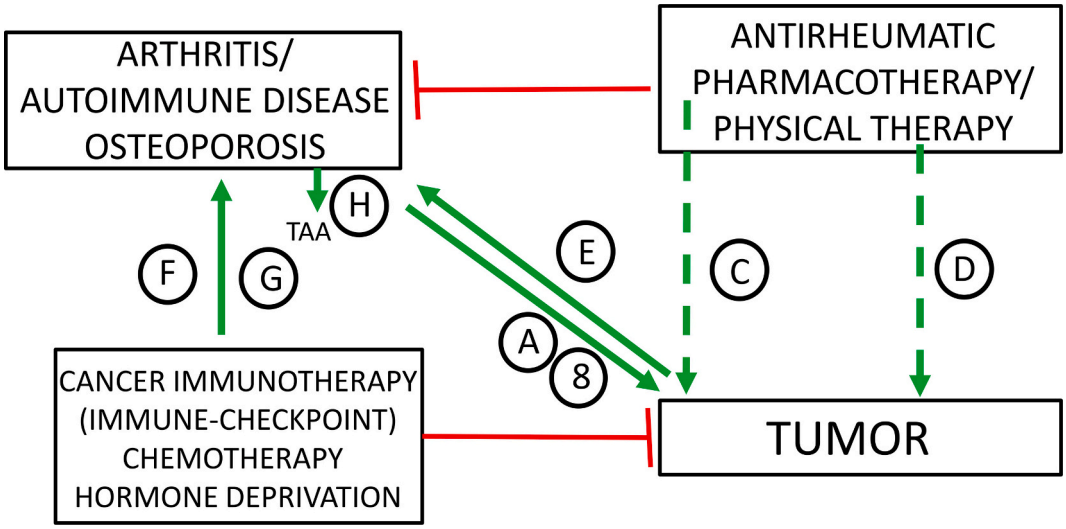

Fig. 1. The oncorheumatology network. Stimulatory processes are in green, while inhibitory mechanisms are in red. (A) RMDs may be associated with secondary tumors. (B) Inflammatory disorders may also be accompanied by increased production of tumor-associated antigens (TAA) with adhesive properties. (C) There is a burning issue of carcinogenicity of antirheumatic drugs. (D) The relationship between cancer and physiotherapy is also controversial. (E) Malignancies and their mediators can cause musculoskeletal paraneoplastic syndromes. (F) Chemotherapy and immunotherapy (immune checkpoint inhibitors) can cause immune-related adverse events. (G) Sex hormone deprivation therapy of breast or prostate cancer can cause osteoporosis. (H) Primary and secondary malignancies of the musculoskeletal system are also important for the rheumatologists.

1. Introduction to oncorheumatology

There is a growing multidisciplinary nature of medicine, which is especially true for rheumatology and oncology. Cooperation between medical specialties may include research on common pathogenic pathways, differential diagnosis, teamwork and “holistic” therapeutic strategies (Fig. 1) [1–3].

Oncorheumatology comprises common mechanisms and clinical aspects of oncology and rheumatic musculoskeletal diseases (RMDs). As discussed later, there are multiple interfaces between the two medical disciplines (Fig. 1; Table 1). Some of the covered topics refer to cancer in patients with RMD, while others address musculoskeletal features in cancer patients. In this review, we will discuss the 8 most relevant pillars of oncorheumatology. These topics may be the most important ones for both researchers and practicing clinicians.

2. Issues of oncology in rheumatic diseases

2.1. Malignancies associated with rheumatic conditions

Research over the past decades has shown that chronic inflammation in rheumatic diseases may stimulate the development of secondary malignancies (Fig. 1, A). Modern antirheumatic therapies have led to significant increases in the lifespan of these patients thus allowing the development of a secondary tumors even after decades. Persistent, chronic inflammation increases the probability of both solid and hematological malignancies [1,3–5].

Table 1
Eight pillars of oncorheumatology.

RHEUMATIC DISEASE → TUMOR
A. Secondary malignancies in rheumatological diseases
B. Soluble tumor antigens in rheumatological diseases
C. Tumor formation / cancer with relapsed rheumatologic drug therapy
D. Non-drug therapy (physiotherapy) in locomotor cancer patients
TUMOR → RHEUMATIC DISEASE
E. Paraneoplastic syndromes
F. Autoimmune / rheumatological disorders with oncotherapy
G. Osteoporosis hormone with deprivation therapy
H. Tumors of the musculoskeletal system

See explanation in the text.

Briefly, in RMDs with autoantibody production (e.g. rheumatoid arthritis, RA; juvenile idiopathic arthritis, JIA; systemic lupus erythematosus, SLE; systemic sclerosis, SSc; Sjögren's syndrome, SS; dermatomyositis, DM), continuous B-cell activation may lead to the development of malignant lymphoproliferative disease in some patients, most notably non-Hodgkin's lymphoma (NHL) [1–13]. This can be aggravated by the simultaneous infection with Epstein-Barr virus (EBV) [14]. On the other hand, targeted therapy with B-cell inhibitors (e.g. rituximab) in these conditions may reduce the likelihood of developing lymphoid tumors (e.g. MALT-lymphoma) [15]. On the other hand, solid tumors develop more frequently in target tissues affected by inflammation [1,2,4,5].

In RA, there is a 12-fold increase in the incidence of lymphoproliferative diseases, while lung cancer is approximately 25% more frequent in comparison to the general population [1,2]. Chronic activation of bronchial-associated lymphoid tissue (BALT) and smoking are involved in the pathogenesis of RA [16,17]. Malignancies of the breast and cervix are also more common, whereas, probably due to the long-term intake of non-steroidal anti-inflammatory drugs (NSAID), there may be lower risk for colorectal and gastric cancers [1,2]. The occurrence of solitary rheumatoid nodules in the lungs may have importance for differential diagnosis [18]. In SSc, there is a 10-fold increase in the risk of NHL [6,7,19]. The risk of lung cancer is 8-times higher. Other solid tumors, such as skin, esophageal, hepatocellular and breast cancer are less frequent with a 1.5-5-fold increase in incidence. Older age, longer disease duration, some autoantibodies and pulmonary fibrosis are independent risk factors for cancer development in SSc [6,7,19–22]. In DM, breast, lung, and gastric cancers are the most common. It is very important to differentiate between secondary tumor associated with myositis and the paraneoplastic syndrome of cancer-associated myositis (CAM) [13,23–25]. In SLE, the incidence of lymphomas, breast, lung cancer, hepatobiliary malignancies and certain types of sarcoma subtypes are increased [1,26]. Risk factors for the development of NHL in SLE include EBV infection, older age, and persistent disease [8,14,26]. In SS, lymphoproliferative disorders are clearly the most common. Lymphadenopathy, prolonged parotitis and parotis swelling, vasculitis, renal involvement, younger age, anemia, neutropenia and lymphopenia predispose to these malignancies [9,11,12,22,27–29]. In JIA, an

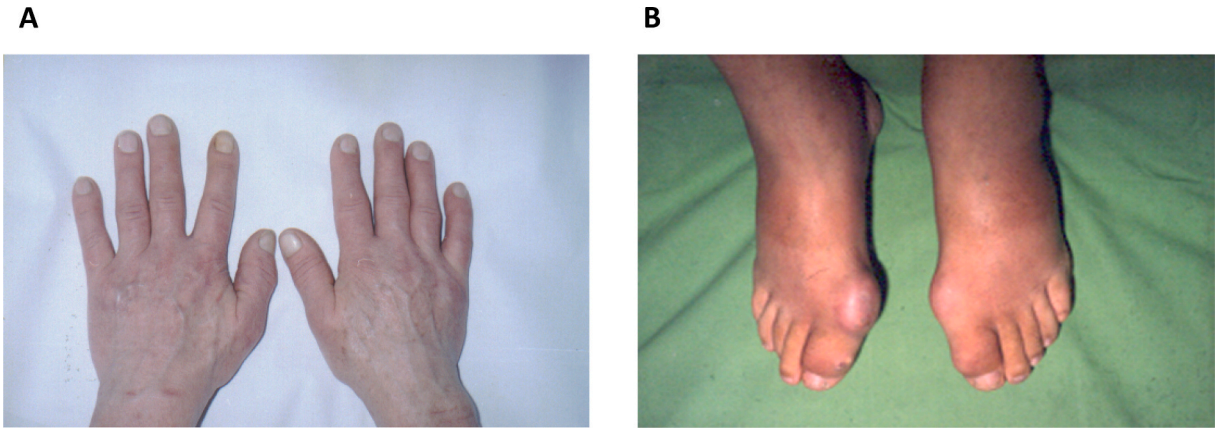

Fig. 2. Clinical examples of paraneoplasia. (A) A 49-year-old female patient developed RA-like (carcinoma) polyarthritis due to ductal breast cancer. (B) Secondary gout developed in a 47-year-old patient with colorectal cancer.

increase in the risk of malignancy was observed in the Swedish registry. Out of 9000 JIA patients, 60 cases of malignancy were described. These included 18 urogenital tumors, 10–10 cases gastrointestinal and skin cancer, as well as 9 cases with lymphoproliferative malignancies. There was no lung cancer. The risk of all malignancies was 2.3-times, while the risk of lymphoma was 4.2 times higher compared to the general population [30]. In contrast, increased risk of malignancies has not been associated with spondyloarthritides (SpA), such as ankylosing spondylitis or psoriatic arthritis. The risk was not higher in patients naïve to or treated with targeted therapies [31–33]. Decades ago, increased risk was occasionally described in SpA patients treated with X-ray or ^{224}Ra irradiation [34].

Another important issue is the relationship between immunodeficiency states and tumors. The major complications of primary immunodeficiency (PID) are infections, autoimmunity, and malignancies. PIDs are clinically rather heterogeneous clinical picture. Defective cellular immunity associated with PIDs also damage anti-tumor immunosurveillance. For example, lymphoproliferative disorders are more common in cases of severe combined immunodeficiency (SCID). Certain infections, oncogenic viruses (EBV, human papilloma virus [HPV]) or other agents that can increase tissue damage and enhance malignant transformation may play a role in the development of PID-associated malignancies. In addition, the genetic mutations associated with PIDs leading to genetic instability may also play a crucial role in tumor formation. Impairment of DNA repair has been observed in ataxia teleangiectasia and Bloom's syndrome. Impaired apoptosis has been observed in autoimmune lymphoproliferative syndrome (ALPS). In Wiskott-Aldrich syndrome, genetically instable tetraploid cells develop due to defective cytokinesis. According to the literature, 4–25% of PID patients may develop malignancies [35]. In an Italian study of 490 PID patients, the incidence of malignancy was 3.6% over 27 years of follow-up. Malignancies were more common in men, probably due to the higher rate of inherited diseases linked to the X chromosome. Two-thirds of the tumors were hematological malignancies, most frequently NHL. About 33% of the cases were solid tumors, most often skin and thyroid cancers [36].

In our previous study, 13 out of 516 RA patients developed malignancies. Out of cancer patients, 6 had lung, two had thyroid, while one had gallbladder, pancreatic, breast and colon cancer. One patient developed cutaneous B-cell NHL. The standardized incidence rate (SIR) for the population ranged from 2.2 to 70.7 [1,2]. Eleven of our 218 SSc patients developed malignancies. These included B-NHL in 3 cases, lung cancer in two cases, breast cancer in two cases, as well as esophageal, skin, cervical and leiomyosarcoma in one case. The population-based SIR ranged from 5.8 to 52.5 [6,7]. Out of 860 patients with SLE, 37 developed tumors. Breast cancer was the most common (11 cases), while gastrointestinal tumors developed in 9 cases, cervical cancer in 5, hematologic malignancies in 5, lung cancer in 4 patients, whereas skin, ovarian and bladder cancer in one patient each. Most cancers developed between 40 and 60 years of age. It should be noted that approximately two-thirds of patients had received azathioprine (AZA) or cyclophosphamide (CYC) known to be carcinogenic (see below) [8]. Out of a total of 309 patients treated with idiopathic inflammatory myopathy (IIM) in our institution, 37 developed malignancies. Of these, 30 were DM and 7 PM. Breast cancer developed most often [24]. Finally, we have investigated the association of autoimmune diseases with lymphomas by assessing lymphoma patients for signs of autoimmunity. (These cases were not paraneoplasiás but rather parallel occurrence of the two diseases.) Out of 421 patients treated with NHL in our center, 32 had autoimmune disease, most often SS. In addition, polymyositis (PM), SSc and RA have also been associated. Out of 519 Hodgkin's disease (HD) patients, 45 had autoimmune background, most often thyroid disease. However, SLE, SSc, and mixed connective tissue disease (MCTD) associations were also identified [10].

With respect to the cellular and molecular pathogenesis of secondary malignancies associated with RMDs, briefly, chronic inflammation leads to tumor development and proliferation through genotoxicity, abnormal tissue repair, enhanced cell proliferation activity, tumor invasion and metastasis (Fig. 2) [4,5,37]. Persistence of inflammatory stimuli and neuroendocrine abnormalities can also maintain chronic inflammation. Subsequently, mutations, defective apoptosis, growth factors, increased angiogenesis, hormonal and epigenetic (environmental) factors may all play a role in the transformation of chronic inflammation into malignancies [4,5,37]. Thus, the role of chronic systemic inflammation is fundamental. For example, in RA, there is a direct association between sustained inflammatory activity and the risk of malignancy [38]. Similar factors are involved in the development of malignant lymphoproliferative disorders following chronic B-cell stimulation [9,11,28]. In systemic autoimmune RMDs, autoantibody persistence may also play a major role. In SSc, autoantibody seropositivity (anti-centromere, anti-topoisomerase I, anti-RNA polymerase III, anti-PM/Scl and anti-RNP) has been associated with the development of malignancy and/or poorer cancer survival [22,39–41].

Most inflammatory mechanisms stimulate the STAT3 (signal transducer and activator of transcription) and NFκB (nuclear factor κB) intracellular pathways. Among inflammatory cells, pro-inflammatory cytokines (tumor necrosis factor α [TNF-α], interleukin 1 [IL-1] and IL-6) produced by myeloid cells, such as monocyte/macrophages) stimulate epithelial cell activation and epithelial-mesenchymal transformation through activation of STAT3 and NFκB. TNF-α, IL-1, IL-13 and transforming growth factor β (TGF-β), on one hand, stimulate the expression of p53 and Myc oncogenes and, on the other hand, enhance tumor angiogenesis by stimulating hypoxia-induced factor 1α (HIF-1α). IL-6 increases the expression of cyclin D1, D2 and B, Bcl-2, Myc and Bcl-

XL oncogenes by STAT3 activation [4].

Malignancies described above may modify their immuno-inflammatory environment. Tumor cells produce growth factors and chemoattractants that eventually inhibit antitumor T-cell immune responses leading to the enhancement of tumor growth. T_H1 cells exerting antitumor responses are replaced by T_H2 and regulatory T-cells (T_{REG}). Macrophage polarization also shifts from pro-inflammatory M1 to M2. In addition, myeloid-derived suppressor cells (MDSC) inhibit cellular immune responses against the tumor [4,5,28,42–44]. In general, during this tumor-derived immunomodulation, tumor cells may intervene in virtually all processes of the anti-tumor inflammatory response and suppress antitumor defense by reprogramming of immune cells [4,44]. First, antigen recognition is impaired because tumor cells produce vascular endothelial growth factor (VEGF) as well as IL-10, IL-6 and TGF-β, all of which inhibit antigen presentation. MDSCs described above have been found in large quantities in the blood and tissue of cancer patients. Tumors attract MDSCs through CCL2, CXCL5, CXCL12 chemokines and stem-cell factor (SCF). MDSCs exert their inhibitory effect on effector T cells through production of IL-10 and TGF-β. In lymphomas, CCL22 chemoattracts T_{REG} cells, which, in turn, inhibit antitumor responses by producing TGF-β, IL-10 and IL-35 [4,42,43].

With respect to the development of lymphoproliferative disorders, transformation to malignancies involves genetic factors (apoptosis genes, gene polymorphisms, MHC allotype), environmental factors (infections, tissue damage, drugs, chemicals, tobacco, asbestos, excessive alcohol intake) and the resulting immunological alterations. The latter are characterized by secondary immunodeficiency, T_{REG} cell defects, alteration of T_H1/T_H2 ratio, abundant cytokine production and increased expression of costimulatory molecules. For example, in SS, these processes lead to epithelial damage (apoptosis, reduced repair, proteolysis) [9,11,28,29,37,45]. With respect to lymphoma subtypes, diffuse large B cell (DLBCL) and marginal zone (MZL) lymphomas are predominant in RA, SS, SLE, and SSc, while T-NHL is more common in RA and SLE. Follicular lymphoma (FL) has been associated with SS and RA [28,45]. The B cell activating factor (BAFF) / Proliferation Inducing Ligand (APRIL) system plays an important role in the pathogenesis of B-cell autoimmunity and lymphomas. As a checkpoint, it also participates in central and peripheral immune tolerance. On one hand, its reduced function favors the development of autoimmune RMDs, such as SS, SLE, RA. On the other hand, overexpression of BAFF/APRIL may lead to polyclonal, then oligo- and monoclonal activation. Belimumab, a BAFF inhibitor, may be utilized in both autoimmune diseases (SLE) and B-cell lymphomas [9,46].

As recently revealed, the microbiome may also play a role in these processes. The role of bacteria in carcinogenesis was already reported in the 19th century, however, this issue has remained controversial ever since. The strongest relationship may be Helicobacter pylori and gastric cancer [4,47]. The association between inflammatory tumor formation and the microbiome was suggested in the mid-2000s. Toll-like receptors (TLR) recognizing microbial antigens and the MYD88 adapter protein are involved in the pathogenesis of colon cancer confirmed [48]. Microbial dysbiosis plays a role in the development of most autoimmune RMDs [17,49]. Further studies are needed to determine the importance of intestinal dysbiosis in the increased risk of cancer associated with RMDs [17,37,49].

2.2. Soluble tumor-associated antigens in rheumatic diseases

Tumor-associated antigens (TAA), which are also assessed in laboratory diagnostics of cancer, are generally glycoproteins that express sialyl- or mucin residues. Most TAAs are involved in tumor adhesion and invasion (Fig. 1, B) [1,50,51]. The most well-known TAAs are shown in Table 2. The table also shows the structure of each TAA and the most commonly associated cancer types [1]. TAAs may be released in soluble form (sTAA) into the blood of patients, which forms the basis for oncological diagnosis [1,50,51].

Table 2
The most relevant tumor-associated antigens and their features.

TAA	Molecular characteristics	Common cancer associations
CEA (CD66)	• 180 kDa gp • sialyl-Lewis X content • adhesion molecule	• colon • pancreas • lung
CA 15–3 (MUC1)	• 300–450 kDa gp • mucin content • adhesion molecule	• breast
CA 19–9	• 300 kDa gp • sialyl-Lewis X content • adhesion molecule	• colon • pancreas • biliary
CA 125 (MUC16)	• 200 kDa gp • mucin content • adhesion molecule	• ovary
CA 72-4	• 400 kDa gp • adhesion molecule?	• gastrointestinal • ovary

Abbreviations: CA: cancer antigen; CEA: carcinoembryonic antigen; gp: glycoprotein; kDa: kilodalton; TAA: tumor-associated antigen.

TAAs may also be expressed by inflammatory leukocytes in addition to tumor cells. We were the first to detect the expression of carcinoembryonic antigens (CEA; CD66 family) on the surface of synovial macrophages of RA patients [52]. Later, several groups showed that sTAAs levels may be elevated in RMDs [1,53,54]. We have measured serum levels of several TAAs in RA, SSc, and SLE [50,51]. In addition to serum level assessments, correlations with inflammatory markers and organ manifestations were also investigated. In RA, CA125 and CA19-9 serum levels were higher compared to healthy controls. Several RA patients had abnormally elevated CA125, CA19-9, and CA15-3 compared to controls. CEA levels correlated with IgM rheumatoid factor (RF), but none of the sTAAs were associated with erythrocyte sedimentation rate (ESR), C-reactive protein (CRP) or disease activity (DAS28) [50]. Several SSc patients had abnormally high levels of CA19-9, CA125 and CA15-3, and numerous SLE patients had increased levels of CEA, CA19-9, CA125 and CA72-4 compared to controls. In SSc, some sTAA levels correlated with renal involvement. Serum CA15-3 correlated with arthritis, antinuclear antibody (ANA) positivity, and CRP. In SLE, CA72-4 correlated with central nervous system (CNS) involvement, whereas CA125 correlated with the SLEDAI activity index [51]. Studies by us and others have suggested that these TAAs may also be involved in the adhesive processes of leukocytes, as well as tumor cells [1,50,51].

The lesson for daily clinical practice is that blood levels of sTAA should be evaluated with caution in patients with RMDs!

2.3. Tumor development, relapse and antirheumatic pharmacotherapy

There has been continuous debate whether conventional synthetic disease-modifying drugs (csDMARD), biological (bDMARD) and targeted synthetic therapies (tsDMARD; tyrosine kinase inhibitors) increase the risk of cancer (Fig. 1, C) [55–58]. As discussed above, systemic inflammation alone promotes tumor formation [4,5,38], so it may be difficult to determine, whether the underlying disease or the treatment would be responsible for increased cancer risk. This question can only be answered by conducting numerous analyzes on data from large registries, also comparing current data with those obtained years ago [38,58–60]. Recent meta-analyses suggest that inflammatory activity of the underlying disease probably outweighs the risk of carcinogenicity of the drug [3,57,60].

Today, CYC, AZA, and cyclosporin A (CsA) are only very rarely used in RA. These csDMARDs may rather be administered in systemic vasculitis, SSc, SLE or IIM. AZA and CYC may be carcinogenic, regardless of the underlying disease [2,3], which has been confirmed by a recent large-scale analysis that excluded the effects of the underlying disease [58]. Based on multiple regression analysis in the UK large registry, the

risk of cancer (RR) for AZA, CYC or CSA was 1.63 (95% CI: 1.05–2.52) [58]. Carcinogenicity is related to dose, route of administration and duration of treatment. For example, CYC may increase the risk of bladder cancer when administered orally. This increased risk is lower when applying parenteral treatment [2].

The most widely used csDMARD in rheumatology is low-dose methotrexate (MTX), which according to recent literature does not increase the risk of developing malignancies [57]. Previously, before the introduction of biological therapy (2016), the incidence of some hamatological malignancies appeared to increase with MTX therapy [61], but it is now likely that this is due to EBV positivity rather than MTX administration. Patients with active inflammation were treated in the early days, usually not in the early stages, so the underlying disease rather than the MTX could be responsible for the increased risk of cancer [56,62].

Although there are relatively few reports, no increase in cancer risk was observed with leflunomide (LEF) [56,63]. Moreover, recent data suggest that leflunomide may even have anticancer effects [64,65].

In the case of biological therapies (bDMARD), it is of particular importance when the survey was conducted. In an early large Swedish study conducted in 2006, a meta-analysis of a total of seven studies from 2000 to 2004 found that the relative risk of malignancies was 3.29 (95% CI: 1.19–9.08) [66]. In those years, treat-to-target strategies have not yet been applied. bDMARD treatment was rather administered to patients with long-term disease, also refractory to other therapies. Already in 2006, it was published and later confirmed that systemic, uncontrolled inflammation rather than bDMARDs may confer the increased risk of cancer [38,67,68]. In later analyses, cancer risk decreased and then disappeared. Analysis of the German registry in 2010 showed only a slightly increased risk of NHL and melanoma malignum in bDMARD-treated patients [69]. In 2012, the risk of solid tumors including melanoma and non-melanoma skin cancer (NMSC), as well as that of NHL was not higher anymore [70]. According to data from the British Registry in 2014, the normalized risk of tumors for the three TNF inhibitors (infliximab, etanercept, adalimumab) available at that time was 0.79–0.89 [59]. These first studies mainly analyzed data on TNF-α inhibitors. In 2017, data from all available bDMARDs (five TNF inhibitors, rituximab, tocilizumab, abatacept) were reported in the Swedish registry and several other studies. Overall, none of the bDMARDs were associated with increased cancer risk [60,71]. Finally, in the 2019 systematic review informing the new EULAR recommendations for the management of RA, five recent studies showed no increased risk of cancer for bDMARDs [57]. Among tsDMARDs, tofacitinib [72–74] and baricitinib [74–76] did not show increased cancer risk based on the Phase III study program and post-marketing data. The most recently approved JAK inhibitor, upadacitinib, was not associated with increased tumor risk in clinical trials [77,78]. With respect to early RA, bDMARDs do not increase cancer risk [79]. Of particular interest are those patients who had a prior history of cancer and subsequently received bDMARD for RA. In the Swedish registry, tumor relapse was determined in hundreds of RA patients who received TNF-α inhibitor therapy after 3–12 months of tumor remission. There was no increased incidence of relapse in the anti-TNF recipients compared to the non-bDMARD-treated controls [80]. In a UK cohort of more than 260 RA patients who developed malignancies, neither TNF-α inhibitors, nor rituximab increased the risk of developing new tumors [59]. In conclusion, unlike AZA or CYC, neither MTX and LEF, nor bDMARDs and tsDMARDs show increased incidence of new tumors or relapses.

2.4. Safety of physiotherapy in rheumatic patients with past or current cancer

Physiotherapy is also a link between rheumatology and oncology. On one hand, the question is whether a rheumatic patient with previous or current malignancy can receive physiotherapy or not (Fig. 1, D) [81]. On the other hand, physiotherapy can also be beneficial for cancer itself [82]. These issues require close cooperation between the various disciplines. One or two decades ago, even the history of cancer was a contraindication for physiotherapy. However, pain is one of the most common complaints of both RMD and cancer patients, it is an essential task. Moreover, physiotherapy is complementary to pharmacotherapy in these patients [81,82].

Based on a meta-analysis of 34 large studies, physiotherapy significantly improves physical function and quality of life in cancer patients [82]. For this reason, it is clear that physiotherapeutic modalities that are not contraindicated in cancer (see below) should also be considered for patients with malignancies [81–84]. If the primary goal is to treat the RMD in patients with malignancies, treatment should be individualized. Patients with current or past tumor should be distinguished. In each case, the individual benefit/risk balance should be considered. There have been few good quality clinical trials in this respect. Most evidence has been gathered in the field of exercise. Conditions that carry contraindications to physiotherapy (e.g. permanent catheters, anemia, polyneuropathy, bone metastasis, etc.) should be consulted with the oncologist. In particular, aerobic exercise is recommended for most patients, which improves the quality of life by alleviating a variety of pathological conditions, such as pain-related mood disorders, chronic fatigue syndrome, sleep disorders, etc. Moreover, exercise improves muscle strength and balance leading to proper motor coordination [81]. The use of other physiotherapy modalities including massage (e.g. lymphatic massage for breast cancer) and electrotherapy (e.g. TENS) are more permissive, although high-evidence studies are not available in this field [81,82]. In post-operative rehabilitation of breast cancer patients, hydrotherapy was very effective and safe [84]. More restrictions may apply for balneotherapy and therapeutic ultrasound. Balneotherapy has been increasingly used in oncological rehabilitation [81,83]. Some treatments, such as shortwave or heat therapy are contraindicated in RMD patients with current tumors as these modalities may promote tumor dissemination by stimulating tumor circulation. On the other hand, as mentioned above, TENS can be used respecting the anatomical location of the malignancy [81].

3. Musculoskeletal aspects of malignancies

3.1. Musculoskeletal paraneoplastic syndromes

Paraneoplasias may occur as a result of distant tumor effects and not by direct contact of the primary malignancy or its metastasis with the affected tissue (Fig. 1, E). Tumor cells, similarly to the way they act in the inflammatory microenvironment (see above), produce hormones, cytokines, peptides, antibodies that trigger an RMD. In addition to these soluble mediators, cellular responses (e.g. cytotoxic T cells) can also trigger paraneoplastic syndromes [85–87]. In addition to RMDs or RMD-like syndromes, paraneoplasias may also be hematological, dermatological, endocrine, nephrological or neurological in nature. Paraneoplastic musculoskeletal syndromes may occur even years before the underlying tumor is identified. These syndromes usually exerts slowly progressive course with asymmetrical symptoms treated by antirheumatic therapy. Sometimes general symptoms (e.g. fever, weight loss, muscular weakness, fatigue) or irresponsiveness to antirheumatic drugs raise the possibility of an underlying malignancy (Table 3) [2,85]. It is also important that paraneoplastic symptoms may improve upon cancer remission or surgical removal and may aggravate upon tumor relapse [2,85,87].

The most relevant musculoskeletal paraneoplasias are listed in Table 3. Clinical manifestations may include arthritis, connective tissue diseases, vasculitides, skin and muscle disorders and metabolic disorders [2,85,88]. The paraneoplastic form of these conditions may mimic the classical disease. In other cases, the “RA-like”, “lupus-like” or “cancer-associated myositis” description suggests that the paraneoplastic syndrome do not fully match the corresponding classical RMD [2,85].

Table 3
Musculoskeletal paraneoplastic syndromes.

Autoimmune (connective tissue) diseases

- Polymyositis, dermatomyositis
- Lupus-like syndrome
- (Catastrophic) antiphospholipid syndrome
- Scleroderma-like syndrome
- Late-onset Raynaud's syndrome

Arthritides

- Hypertrophic osteoarthropathy
- Carcinoma polyarthritis (RA-like)
- Relapsing polychondritis
- RS3PE syndrome
- Palmar fasciitis polyarthritis

Vasculitides

- Atypical polymalgia rheumatica
- Erythema nodosum
- Cryoglobulinemic vasculitis

Skin- and muscle diseases

- Dermatomyositis
- Lambert-Eaton syndrome
- Palmar fasciitis
- Panniculitis
- Eosinophilic fasciitis

Metabolic diseases

- Gout
- Reflex sympathetic dystrophy
- Tumor-associated osteomalacia

Showing a few examples of paraneoplastic RMDs, CAM is not identical with secondary tumors associated with IIM described above. Myositis, is more common in DM than in PM, generally over the age of 50 years. It is most commonly associated with lung, breast, ovarian, colorectal and nasopharyngeal cancer, melanoma and NHL. Compared to classical DM, more severe skin symptoms and diaphragmatic involvement are characteristic [13,23]. Lupus-like syndrome is most commonly associated with breast, ovarian cancer, mesothelioma, and hairy cell leukemia (HCL). Polyserositis, Raynaud's syndrome and antinuclear antibody (ANA) positivity are important features [85]. SSc-like disease develops along with lung, breast and ovarian cancer and is characterized by anti-topoisomerase I (anti-Scl70) antibody positivity [19]. Antiphospholipid antibodies in solid tumors have been associated with thromboembolic complications [89,90]. We have reported two cases of catastrophic antiphospholipid syndrome (CAPS) with generalized thromboembolism associated with endometrial and gastric cancer [91,92]. Paraneoplastic polymyalgia rheumatica (PMR) occurs asymmetrically at a younger age (< 50 years) and systemic inflammation is not pronounced (ESR < 40 mm / h) as in classical PMR [85]. RA-like "carcinoma polyarthritis" occurs at an older age and is characterized by faster progression, as well as seronegativity, asymmetric nature and lower limb dominance (Fig. 2A) [1]. Secondary hypertrophic osteoarthropathy (HOA) caused by lung cancer or mesothelioma is characterized by the clubbing of fingers that develop due to periosteal proliferation [93]. RS3PE syndrome (relapsing seronegative symmetric synovitis with pitting edema) occurs in older men with hands and feet affected. This disease is seronegative, non-erosive, but is characterized by systemic inflammation [2]. Palmar fasciitis or palmar fasciitis with polyarthritis are associated with swelling, warmth, redness of the palms, and may mimic Dupuytren's contracture [2]. Eosinophilic fasciitis, a scleroderma-like disease may be associated with lymphoproliferative disorders [85]. Among metabolic diseases, secondary hyperuricaemia and gout are associated with disseminated solid tumors, lymphoproliferative disorders and their chemotherapy (Fig. 2B) [1]. The paraneoplastic form of reflex sympathetic dystrophy may be observed in lung, ovarian, and pancreatic cancer. If the patient does not have a history of trauma, stroke or cardiovascular disease, and underlying tumor should be searched for [85].

As far as cellular and molecular pathogenesis is concerned, finger clubbing in HOA is a consequence of neovascularization induced by tumor-derived angiogenic mediators, primarily VEGF and platelet-derived growth factor (PDGF). Angiogenesis leads to soft tissue edema, later fibrosis and periosteal thickening [85]. Pro-inflammatory cytokines produced by the tumor induce a RA-like pattern of carcinoma polyarthritis. Matrix metalloproteinases (MMP-3), also released by the tumor, play a role in the edema associated with R3SPE syndrome [2,85]. CAM is aggravated by anti-TIF1 antibody produced by the tumor [23]. Crosstalk between bone metastases and skeletal muscle has also been described. Metastasizing breast cancer cells produce activin A, TGF-β and insulin-like growth factor I (IGF-I) and are involved in the development of muscle pain and weakness. In turn, skeletal muscle cells stimulate the growth of bone metastases through myokines (IGF-I, IL-6, fibroblast growth factor 2 [FGF-2]) [94]. Finally, in tumor-induced osteomalacia, stromal mesenchymal cells release FGF-23, which enhances renal phosphate excretion and causes osteomalacia [85].

3.2. Autoimmune side effects of oncotherapy

3.2.1. Conventional chemotherapy, cytokines and kinase inhibitors

Immune-related adverse events (IRAE) may occur during standard chemotherapy or cytokine therapy (Fig. 1, F; Table 4). Musculoskeletal symptoms usually appear a few weeks or months after the initiation of treatment. The symptoms (arthralgia, myalgia, morning joint stiffness, periarticular swelling of small joints, ankles and knees) are usually non-inflammatory, migratory and self-limiting. These IRAEs are non-erosive and respond well to NSAIDs [2,95–97]. CYC, 5-fluorouracil (5-FU), tamoxifen, MTX and cisplatin are most frequently triggering such IRAEs. Bleomycin, vinca alkaloids and cisplatin can cause Raynaud's syndrome, while 5-FU, cisplatin, CYC, MTX, aromatase inhibitors and tamoxifen may induce arthralgia and/or myalgia [95,97]. The effects of aromatase inhibitors and anti-androgens on osteoporosis will be discussed later [98]. Among cytokines, IL-2 may induce arthralgia, myalgia, and interferon α (IFN-α) treatment may cause RA- or SLE-like syndromes [96]. Kinase inhibitors, such as BRAF and MEK inhibitors may cause mild, moderate, or severe arthralgia in 40% of cases [99]. Initially, paracetamol or NSAIDs can be administered, while in more severe cases, corticosteroid treatment may be needed (Table 4) [95,99].

3.2.2. Immune checkpoint inhibitors

Immune checkpoints are cell surface proteins that control the activation of the immune system. With respect to anti-tumor immunity, the

Table 4
Musculoskeletal side-effects of chemotherapy and cytokine therapy in oncology.

Compound	Side-effects
Bleomycine	Raynaud's syndrome Skin thinning
Vinblastine, vincristine	Raynaud's syndrome
Cisplatin	Raynaud's syndrome Arthralgia, myalgia
Aromatase inhibitors and anti-androgens	Arhralgia, myalgia Osteoporosis
5-fluorouracil	Arthralgia, myalgia
Cyclophosphamide	Arthralgia, myalgia
Methotrexate (high-dose)	Arthralgia, myalgia
Tamoxifen	Arthralgia, myalgia
Interferon-α	SLE-, RA- or PM-like disease
Interleukin 2	Arthralgia, myalgia
Tyrosine kinase (BRAF, MEK) inhibitors	Arthralgia, myalgia

Abbreviations: PM: polymyositis; RA: rheumatoid arthritis; SLE: systemic lupus erythematosus.

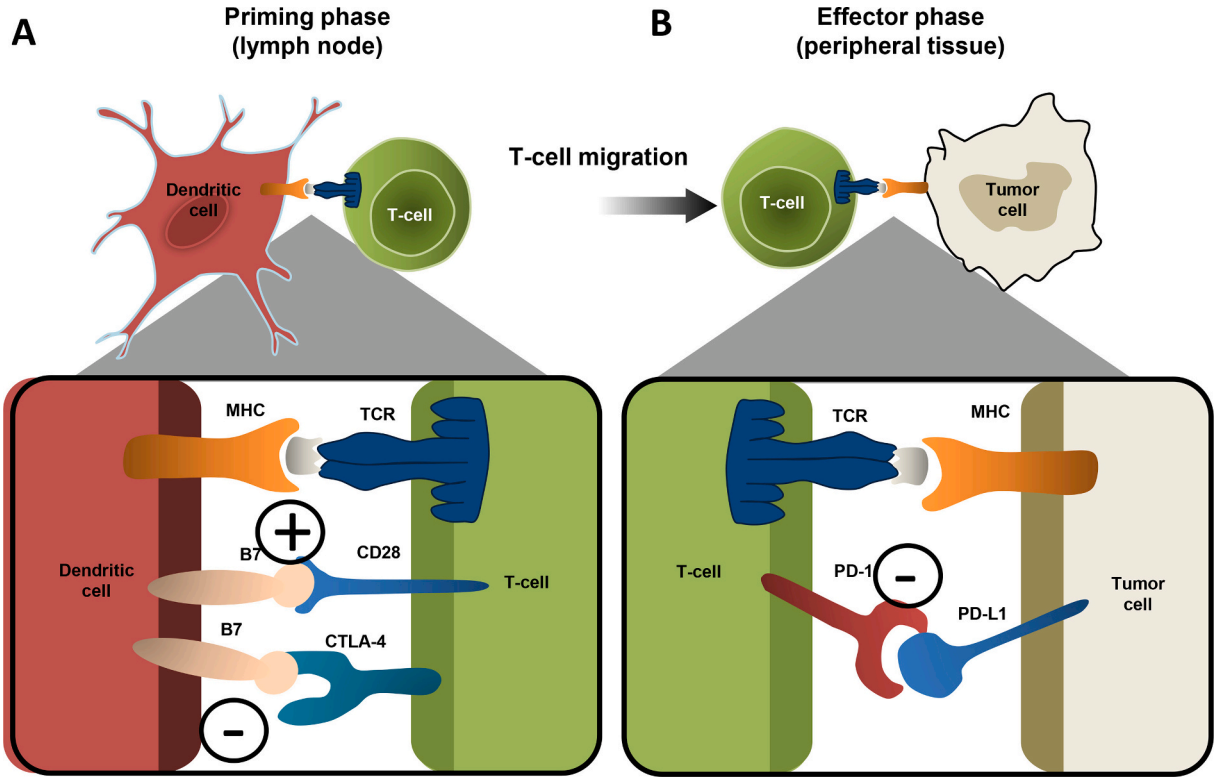

Fig. 3. Involvement of immune checkpoints in antitumor immunity. (A) During the priming phase, T-cell undergoes a "learning phase" in the lymph nodes. Antigen-presenting dendritic cells (DC) present the tumor antigen. In addition to the known T-cell receptor-MHC binding, costimulation is also required. CD28 binding to B7.1 (costimulation) results in tumor antigen recognition. CTLA4-B7.2 binding, in turn, induces coinhibition and consequent immune tolerance. (B) Activated T-cells migrate to the peripheral (tumor) tissue and initiate tumor defense. However, PD-1-PD-L1 interaction also results in coinhibition, which weakens T-cell anti-tumor response. Further explanation in the text [100].

initial basic step of the immune response is when antigen presenting cells (APC; e.g. dendritic cells [DC], macrophages) present the tumor antigen to T-cells. In turn, T-cells recognize and, ideally, destroy the tumor cell (Fig. 3) [100–102]. It is known that in addition to the described primary recognition mechanism, antigen recognition requires a second, so-called costimulatory signal. When the APC B7-1 (CD80) antigen binds to the CD28 molecule of the T cell, a positive signal (costimulation) is generated and the T-cell is activated. However, if the B7-2 (CD86) molecule on the APC binds to the cytotoxic T-lymphocyte antigen 4 (CTLA4) on the T-cell or the APC programmed death ligand 1 (PD-L1) molecule binds to the T-cell PD-1 receptor, a coinhibitory signal is triggered and T-cell anergy develops and antitumor immunity will be insufficient (Figs. 3 & 4 [100,103]. Therefore, in order to successfully restore antitumor immunity, we must block either CTLA4- or PD-1-mediated coinhibition ("inhibition of inhibition") (Fig. 4) [100,103]. Monoclonal antibodies to CTLA4, PD-1, or PD-L1, which reverse coinhibition and thus enhance antitumor T-cell responses are called immune checkpoint inhibitors (ICI) (Fig. 4) [101–104]. Recently, ICI therapy has become a major breakthrough on tumor immunotherapy. Currently available ICIs include the CTLA4 inhibitor ipilimumab, the PD-1 inhibitors nivolumab and pembrolizumab, and the PD-L1 inhibitors atezolizumab, avelumab and durvalumab. Approved indications of these agents and their combinations with other antineoplastic drugs include primarily metastatic melanoma and lung cancers, however, they are also registered for the treatment of head and neck, liver, kidney, bladder cancer and Hodgkin's disease [101,102,104,105].

The major association of ICI treatment with rheumatology is the possible development of IRAEs (Fig. 1, F; Table 5). Because ICIs do not target the tumor cell itself, but rather the host immune system, the notable efficacy of ICIs in different types of malignancies may be associated with development of IRAEs (Fig. 4) (reviewed in [102–112]).

In order to further understand the pathogenesis of ICI-induced IRAEs, we should briefly discuss the major intracellular signaling pathways influenced by ICIs. In T-cells, PD-1 and PD-L1 inhibition stimulates mTOR (cell growth and protein synthesis), Bcl-xL (cell survival), and Ras (cell proliferation) signaling. In addition, metabolic changes (enhancement of glycolysis) occur. Thus, ICIs stimulate the growth, proliferation, and survival of T-cells involved in the anti-tumor immune response. In addition, they also shift T-cell metabolism to improve their effector function. Consequently, ICI inhibitors stimulate the anti-tumor immune response, but also autoimmune processes (Fig. 4) [101,103]. In addition, a dysbalance between T_H17 and T_{REG} cells is also involved in the development of IRAEs. Increased expression of PD-1 and PD-L1 favors T_{REG}, whereas PD-1 deficiency or inhibition favors T_H17 differentiation [101,103]. Other pathogenic factors include certain autoantibodies, as well as pro-inflammatory cytokines (TNF-α, IL-1, IL-6, IL-17). Activation of the interferon (IFN) signature has also been demonstrated [101,103]. In autoimmune animal models, deficiency of the *PD1* gene or inhibition of PD-1 and PD-L1 increased the development of various types of arthritis, SLE, autoimmune encephalomyelitis, cardiomyopathy and diabetes [103,113,114]. In human arthritides, such as RA and PsA, increased expression of PD-1 and PD-L1 was observed compared to healthy subjects, suggesting a counter-regulatory mechanism in order to attenuate the development of autoimmunity [113,115]. Consequently, the use of ICI inhibitors may suppress this counter-regulation, which favors autoimmunity [113]. Recently, the genetic role of HLA-DRB1 ("shared epitope") has also been confirmed in ICI-induced arthritis [116]. Finally, the next generation of novel coinhibitory molecules (e.g. TIM-3, LAG-3, TIGIT, BTLA, VISTA) has also been identified. This class of checkpoints may also have relevance for the development of IRAEs [117].

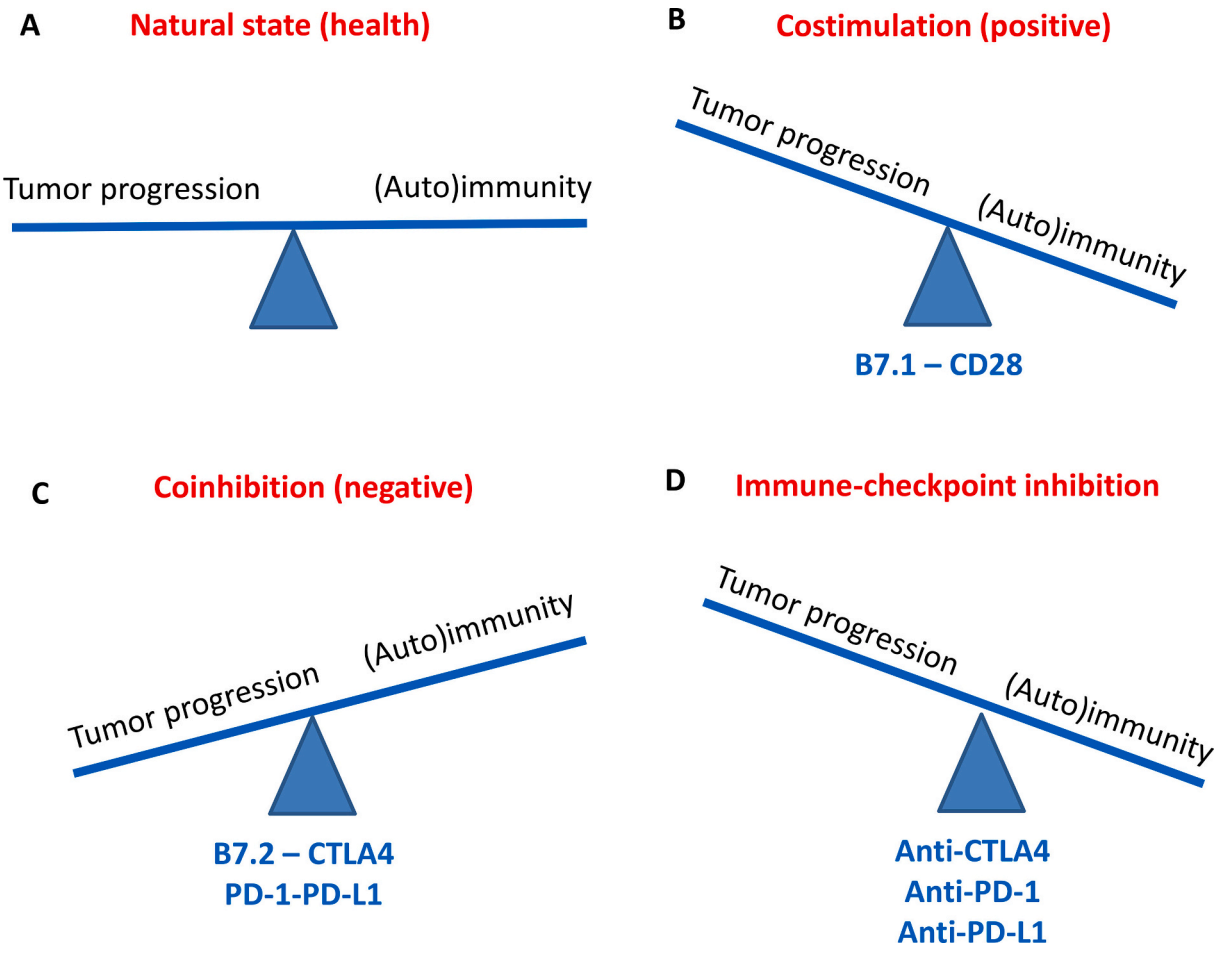

Fig. 4. Brief explanation of the balance and dysbalance of tumor progression and antitumor immunity. (A) In healthy individuals, antitumor immunity inhibits tumor development. (B) Costimulation based on the binding of CD28 to B7.1 enhances cellular immune responses including antitumor immunity and autoimmunity. (C) Coinhibition by CTLA4- and PD-1-mediated pathways suppresses antitumor immunity leading to enhancement of tumor progression. (D) Administration of immune-checkpoint inhibitors reverses the enhancement of coinhibition resulting in an effective antitumor response but also the possible development of autoimmune side-effects [100].

Table 5
Autoimmune side effects of immune-checkpoint inhibitor therapy [102,110,111].

Therapy	Autoimmune disease	Prevalence
CTLA4 inhibitor	arthralgia and arthritis	5–16%
	myalgia and myositis	2–18%
	sicca syndrome	3–4%
	dry eyes	3–4%
	dry mouth	7%
PD-1/PD-L1 inhibitors	arthralgia and arthritis	5–16%
	myalgia and myositis	2–18%
	sicca syndrome	3–11%
	dry mouth	3–11%
comnination therapy	arthralgia and arthritis	10,5%
	myalgia and myositis	1%
	sicca syndrome	3–4%
	dry mouth	3–4%

Abbreviations: CTLA: cytotoxic T lymphocyte antigen; PD: programmed death; PD-L: programmed death ligand.

With respect to clinical aspects of IRAEs, the incidence of side effects of ICIs is much lower than that of conventional chemotherapies (Table 5). Typically, IRAEs start relatively early, often within the first 3 months after starting the ICI therapy. Later these events occur much less frequently [102,110,111]. The frequency of the various RMDs that present as IRAEs is summarized in Table 5 [102,110,111]. In addition to RMDs, other IRAEs may affect almost all organs, including the respiratory (pneumonitis), gastrointestinal (colitis), endocrine (thyroid, pituitary, diabetes), nervous system (polyneuropathy, demyelination, aseptic meningitis, Guillain-Barré syndrome), skin (itching, rash), and more rarely the eyes (uveitis, keratitis, dacryoadenitis, retinopathy), kidneys (nephritis) and liver (hepatitis) [102,108,110,111].

IRAEs should be documented and regularly monitored during therapy and follow-up [118–123]. Numerous therapeutic recommendations by various societies have been published from the perspective of both rheumatologists and oncologists [111,119–122]. Although there might be slight differences between these recommendations, Table 6 summarizes the treatment principles if IRAEs [102,111,119,122,123]. In general, in Grade 1 (mild) IRAE, ICI therapy can be continued (with the exception of a few hematological and neurological abnormalities), but close monitoring is required. ICI treatment should be temporarily suspended and low-dose (0.5–1 mg/kg) corticosteroids administered for a minimum of 4–6 weeks in Grade 2 (moderate) IRAE. In Grade 3 (severe) IRAE, higher corticosteroid dose (1–2 mg/kg) should be introduced. ICI therapy should be terminated. Finally, in Grade 4 (life-threatening) abnormalities, termination of immunotherapy, hospitalization of the patient, and administration of high-dose (2–4 mg/kg) systemic corticosteroids are required. In Grade 3 or 4 IRAE, if there is no improvement despite corticosteroid treatment, other immunosuppressive agents, such as csDMARDs or bDMARDs should be introduced. Complications should be monitored regularly

Table 6
Recommendation for the management of immune-checkpoint inhibitor-related autoimmune-rheumatic adverse events [102,111,120].

Severity grades	First-line therapy	Second-line therapy	Immune-checkpoint inhibitor therapy
Grade 1 (mild)	NSAID; intraarticular corticosteroid		continue
Grade 2 (moderate)	corticosteroid (0.5–1 mg/kg/day); intraarticular corticosteroid		transiently suspend
Grade 3 (severe)	corticosteroid (1–2 mg/kg/day)	methotrexate, sulfasalazine, leflunomide, chloroquine, bDMARD	discontinue
Grade 4 (life-threatening)	corticosteroid (2–4 mg/kg/day)	methotrexate, sulfasalazine, leflunomide, chloroquine, bDMARD	discontinue

Abbreviations: bDMARD: biologic disease-modifying drug; NSAID: non-szeroidal anti-inflammatory drug.

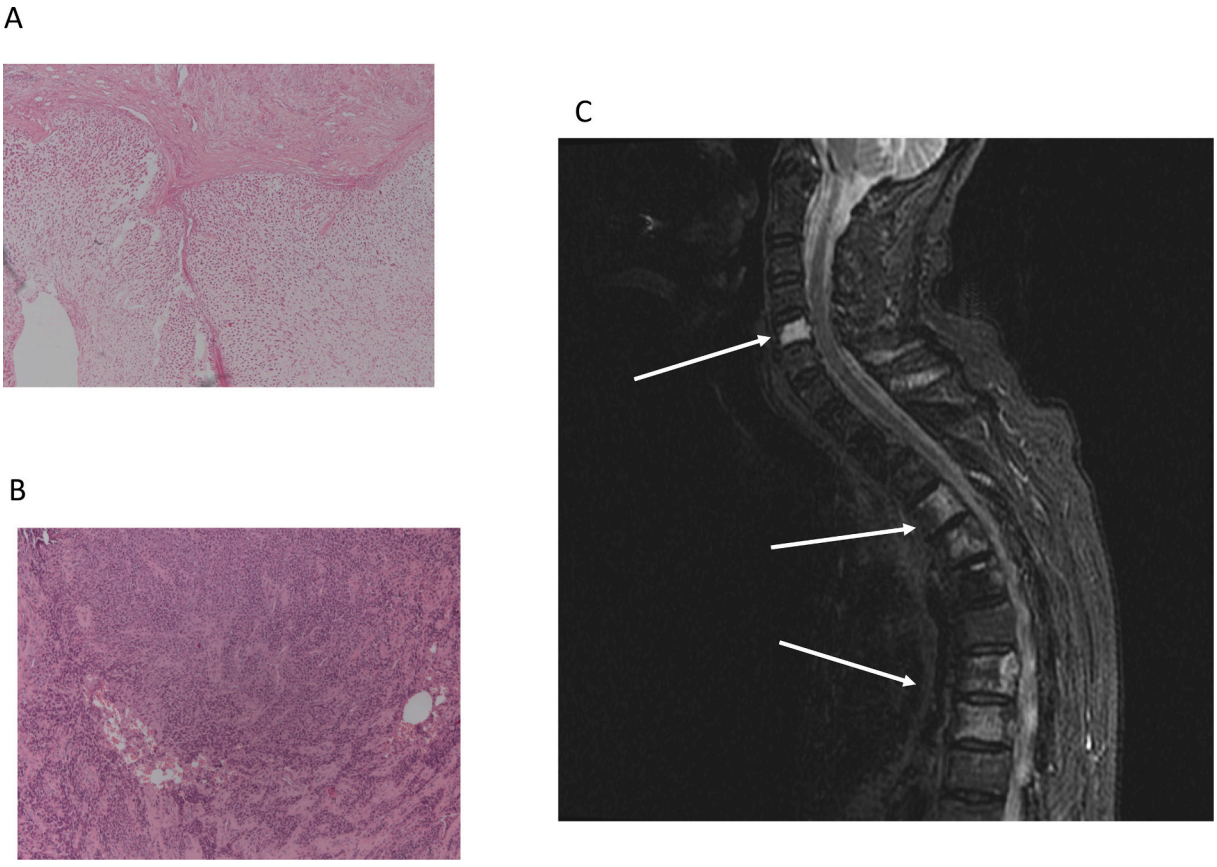

Fig. 5. Clinical examples of musculoskeletal malignancies in our practice. (A) Chondrosarcoma of the rib. Connective tissue infiltration of malignant chondrocytes (courtesy of Willian Yi-Che, Kenézy Hospital, Department of Pathology, Debrecen). (B) Ewing sarcoma of the humerus. Malignant "small blue cell" tumor tissue (courtesy of Willian Yi-Che, Kenézy Hospital, Department of Pathology, Debrecen). (C) Multiple vertebral metastases of prostate cancer (arrows).

(Table 6) [102,111,119,122].

Finally, one importance of this topic is that James P. Allison and Tasuku Honjo won the Nobel Prize for Medicine in 2018 for describing the CTLA4- and PD-1/PD-L1-dependent immune checkpoint pathways [124].

3.2.3. Osteoporosis after sex hormone deprivation therapy

Both female and male sex hormones are known to play a role in the maintenance of bone homeostasis. For example, TGF-β inhibits osteoblast and stimulates osteoclast apoptosis through estradiol. Estrogens also inhibit IL-1- and IL-6-mediated bone loss and stimulate OPG production. Androgens have similar effects [98]. Aromatase inhibitors and antiandrogens are included in the treatment of breast, prostate and other genital tumors [98]. Inhibition of these sex hormones leads to increased bone resorption and osteoporosis. In breast cancer, aromatase inhibitors, and in prostate cancer, androgen deprivation therapy have been associated with osteoporosis and increased risk of fracture (Fig. 1, G) [98,125].

With respect to mode of action, both the bone-resorbing effects of the tumor itself and the hormone deprivation therapy simultaneously cause osteoporosis. Bone resorption is associated with the release of soluble mediators, such as IGF—I, TGF-β, PDGF, bone morphogenetic protein (BMP) and the CXCL12 chemokine that enhance tumor growth. In turn, mediators produced by growing tumor further stimulate bone resorption and the formation of bone metastases [98].

In clinical practice, cancer patients undergoing sex hormone deprivation therapy should be regularly screened for osteoporosis and treated appropriately. Clinical data are mostly available for bisphosphonates (zoledronate, ibandronate) and the RANKL inhibitor antibody, denosumab [98,125–127]. In breast cancer, tamoxifen or anastrozole added to GnRH analogue showed significant bone loss after 24–26 months, which could be prevented by zoledronate [125]. Zoledronate prevented bone loss if initiated in parallel with the aromatase inhibitor but not if administered with delay [126]. Similar favorable

data are available with denosumab [98,127]. In addition, calcium and vitamin D supplementation, as well as regular exercise are recommended [98].

3.2.4. Malignancies of the musculoskeletal system

Malignancies of the musculoskeletal system is also a part of oncorheumatology (Fig. 1, H). In this review, we do not aim to provide details of this vast field in oncology. Here we briefly summarize clinically important information [128,129].

Histologically, tumors of the musculoskeletal system represent a very heterogeneous group. Sarcomas are tumors of mesenchymal origin that can originate from any non-hemopoietic mesodermal tissue (bone, cartilage, fat, muscle, tendon, connective tissue, vessel). Mesenchymal transformation has several biomarkers, such as vimentin, desmin, actin, MyoD1, myoglobin, myogenin and p63 [128–130].

These malignancies account for 0.5–1% of all solid malignancies. They may develop at any age but are more common in childhood. There is no gender dominance. The prognosis of sarcomas is very poor: the rate of local recurrence after surgery and that of distant metastases occurring after 5 years are around 50%. No clear etiological factors are known. Some sarcoma types may be linked to chromosomal aberrations and gene defects. Other possible causes include preservatives, herbicides, prior radiation therapy, foreign body implantation, chronic lymphedema, viral infection, immunodeficiency states, trauma [128–131].

In general, sarcomas are divided into two main groups. Soft tissue sarcomas include rhabdomyosarcoma (20–25%), pleomorphic, non-differentiated sarcoma (15–20%), fibrosarcoma (15–19%), liposarcoma (14–18%), synovial sarcoma (5–10%) leiomyosarcoma (5–6%), chordoma (5%) and giant cell bone tumor (3–5%). Bone sarcomas include osteosarcoma (35%), chondrosarcoma (25%) and Ewing's sarcoma (16%). Rare forms include chondroblastoma, chondromyxoid fibroma, osteoblastoma, Langerhans cell histiocytosis, adamantinoma [128–131]. Some of our own cases are shown in Fig. 5.

Distinction from bone metastases is important for differential diagnosis. For example, breast and prostate cancers are mainly characterized by osteolytic and osteoplastic metastases, respectively. Mixed metastases may also occur [2,131].

With respect to treatment, obviously, the tumor type must first be confirmed histologically. Then surgery has still the highest curative rate. After detailed staging, combination therapy may give the most favorable results. If the patient's condition permits, several cycles of chemotherapy as neoadjuvant treatment are administered weeks before the planned surgery. After adequate wound healing, postoperative adjuvant chemotherapy is administered. Applying this combination, relapse rate is low, usually below 10% [128,129,132]. Sarcomas are usually resistant to irradiation. Due to numerous side effects, it is only used in palliative indications [129,131]. The most widely used chemotherapeutic agents are still anthracyclines and ifosfamide. They drugs may be administered in monotherapy or in combination. Bisphosphonates or denosumab, as well as radioisotopes (e.g. Multibone beta, ^{223}Ra alpha) may be used to treat bone metastases. Targeted therapies carry hope for the future. The most promising treatment options include mTOR inhibitors, pazopanib, trabectedin, aromatase inhibitors, denosumab, gefitinib/erlotinib, imatinib/sunitinib and some others [129–131].

Acknowledgements

The work is the European Union Social Fund TAMOP-4.2.4.A/2-11/1-2012-0001 National Excellence Program (Sz. Z.); and with the support of the European Union GINOP-2.3.2-15-2016-00015 (Sz.Z.).

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