# Malignancy and rheumatic disorders: a review

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## Abstract

**Background:** Some malignancies may present or be associated with musculoskeletal manifestations. Additionally, therapies for malignancies can cause rheumatic disease syndromes.
**Objective:** The aim of this literature review is to address the various malignancies and their pharmacologic therapy that are associated with an increased risk of rheumatic disease.
**Data source:** The literature review uses medical science-based literature published locally and internationally on the risk of rheumatological diseases in patients with malignancies and the use of cancer chemotherapeutic agents.
**Conclusion:** Malignancies have been associated with a number of rheumatic manifestations either of the illness itself or as paraneoplastic syndromes. Similarly various rheumatological diseases may occur as a result of treatment.

**Key words:** Rheumatic diseases, Cancer, Chemotherapy, Immune-therapy, Malignancy, Screening

## Introduction

There is a bidirectional relationship between rheumatological diseases and cancer. Certain rheumatic disorders and their treatment may increase the risk of malignancy. Conversely, some malignancies may present or be associated with musculoskeletal manifestations. Additionally, therapies for malignancies can cause rheumatic disease syndromes[1,2]. The rheumatic presentation of malignant disorders and rheumatic symptoms caused by anti-tumour therapies will be reviewed here.

## Malignant diseases with musculo-skeletal manifestations

A variety of malignancies can have musculoskeletal manifestations[3]. The most common manifestation is bone pain that occurs more frequently with in patients with bone metastasis and multiple myeloma.

The articular and systemic autoimmune phenomena occur not only as paraneoplastic rheumatologic syndromes but also as a direct consequence of some malignancies like lymphoproliferative and myelodysplastic disorders. About 25% of patients who had been admitted to hospital with rheumatological disease had occult malignancy[4]. The rheumatic symptoms usually improve on tumour remission.

## Lymphoma

Articular symptoms in lymphoma may result from hyperuricemia that manifests as secondary gout due to increased cell turnover. It can also occur due to infiltration of the synovium by abnormal lymphomatous cells[5]. However, joint infiltration by lymphomatous cells is unusual and tends to occur primarily with T cell lymphomas. Synovial fluid analysis shows atypical lymphocytes while synovium biopsy will show infiltration by lymphoma cells[6].

In addition, some clinical features of lymphomas may mimic systemic inflammatory and autoimmune rheumatic disorders. For example, patients with angioimmunoblastic T cell lymphoma present with arthritis, skin rash, Coombs-positive haemolyticanaemia, fever and weight loss which may be suggestive of systemic lupus erythematosus or Still's disease. Similarly, patients with predominantly extra nodal lymphoma may be confused to be having granulomatosis with polyangiitis or lymphomatoid granulomatosis.

## Large granular lymphocyte syndrome

Large granular lymphocyte syndrome is a chronic lymphoproliferative disease characterised by lymphocytosis, bone marrow infiltration, splenomegaly, neutropenia and anaemia. Thirty percent of the patients also have Rheumatoid Arthritis[7]. This could also fulfil the clinical criteria for Felty syndrome. Furthermore,

due to the clonal lymphocyte expansion, large granular lymphocyte syndrome can lead to development of eosinophilic fasciitis[8].

## Leukaemia

Four percent of adults and 14% of children with leukaemia will present with either symmetrical or migratory polyarthritis[9,10]. Acute lymphoblastic leukaemia is the predominant leukaemia causing arthritis in children, while in adults it is acute lymphoblastic leukaemia, acute myeloid leukaemia and chronic lymphocytic leukaemia.

The pain in leukaemic arthritis is severe and unresponsive to antirheumatic medications[11]. Radiographs reveal more osteopenia and earlier lytic lesions than one would expect.

The joint manifestations in leukaemia are due to synovial infiltration by leukemic cells, hemarthrosis and periosteal or capsular lesions. Synovial biopsy may be diagnostic but due to the patchy nature of neoplastic involvement, it can be negative. This can be complemented by immunocytologic analysis of the synovial fluid. Leukemic synovitis is a sign of aggressive disease and should prompt immediate leukaemia directed therapy[12].

## Myelodysplasia

About a quarter of patients with myelodysplasia have autoimmune abnormalities[13]. The most common manifestation is polyarthritis that mimics rheumatoid arthritis. Most of the patients are seronegative for Rheumatoid Factor (RF) and anti-citrullinated peptide antibody, neither do they show joint erosion on radiography. The arthritis precedes the diagnosis of myelodysplasia in about 50% of the cases. Myelodysplasia should be suspected if there is persistent cytopenia and raised acute phase reactants despite adequate control of the arthritis[14,15].

## Rheumatic disorders associated with treatments for malignant disease

There are a number of rheumatological disorders that may arise because of treatment, especially with chemotherapy. These disorders are referred to as post chemotherapy rheumatism or chemotherapy related arthropathy[16,17]. Furthermore, there are concerns that radiation therapy may also increase the risk of rheumatologic diseases and with rheumatologic diseases have higher risk of getting radiation toxicity. Additionally, cancer immunotherapies, especially immune checkpoint inhibitors have been associated to a number of rheumatic and musculoskeletal disorders. These will be further discussed below.

## Chemotherapy related musculoskeletal disorder

### Aromatase Inhibitors

Aromatase Inhibitors (AIs) are used in the treatment of hormone receptor positive breast cancer. The drugs in this class include letrozole, anastrozole and exemestane. They suppress plasma oestrogen levels by inhibiting aromatase. Aromatase is an enzyme that is responsible for the peripheral conversion of androgens to oestrogens.

AIs are associated with a constellation of musculoskeletal symptoms ranging from arthralgia, joint stiffness, bone pain to Carpal tunnel syndrome. These constellations of symptoms are collectively known as AI associated musculoskeletal syndrome (AIMSS)[18-22]. AIMSS occurs in up to 50% of the patients and are severe in a third of the patients[20]. This leads to discontinuation of treatment in 15 – 20% of the patients[19-22].

The aetiology of AIMSS is not known but decreased oestrogen levels may play a role[21-24]. Furthermore, about half of the women who develop AIMSS have pre-existing musculoskeletal disorder[22].

The following strategies may aid in management of AIMSS

1. *Exercise and Nonsteroidal Anti-inflammatory Drugs (NSAIDs):* The initial strategy for managing AIMSS includes exercise and NSAIDS. In the HOPE trial, 121 postmenopausal women with AI associated arthralgias were randomly assigned to an exercise regimen or to usual care[25]. The patients in the exercise regimen had reduction in both their worst pain score (20% versus 1%) and pain severity (21% versus 0%) compared with usual care. A greater reduction in worst pain score (25% versus 14%) was noted in those patients who attended more than 80% of the exercise session. In addition, the primary treatment of AIMSS often begins with administration of NSAIDs, as they constitute mainstay treatment of pain.
2. *Temporary discontinuation of AI, followed by initiation of a different AI:* For women, in whom conservative measures including exercise and NSAIDs have been unsuccessful, we can discontinue treatment for two to eight weeks and then re-initiate with a different AI[26].
3. *Duloxetine:* Duloxetine is the next option if symptoms persist despite the above measures. In the SWOG S1202 trial, those patients randomised to duloxetine experienced improvement in joint pain relative to placebo[27].
4. *Acupuncture:* This is a non-pharmacologic method used in the management of AIMSS. Although the benefits are not so large, we consider as an appropriate

option for those patients who have been unsuccessful with the above steps or for those who cannot tolerate duloxetine[28].

5. *Switch to tamoxifen:* Tamoxifen is a Selective Oestrogen Receptor Modulator (SERM). It inhibits growth of breast cancer cells by competitive antagonism at the oestrogen receptor. Although AIs have a modestly better outcome than tamoxifen, some women may tolerate the toxicities of tamoxifen better than the toxicities of AI.

## Bleomycin

Bleomycin has been associated with systemic sclerosis. It was noted to induce skin and lung fibrosis in animal models[29]. Similarly, there have been several cases of systemic sclerosis with Raynaud's phenomenon in patients undergoing treatment with bleomycin[30]. It is postulated that bleomycin causes chromosomal breaks by oxidation that leads to formation and release of autoantigens that leads to development of systemic sclerosis[31].

## Taxanes

In addition to causing arthralgia and myalgia in about 60% of patients, taxanes cause Subacute Cutaneous Lupus Erythematosus (SCLE). SCLE is manifested by annular or polycyclic, photo distributed erythematous, and scaling lesions. Both phototoxicity and autoimmunity play a role in the pathogenesis as evidenced by presence of immunoglobulin G deposits in the keratinocytes and presence of anti-Ro/SSA antibodies[32].

## Gemcitabine

There have been a couple of case reports that associate gemcitabine with causing systemic sclerosis with Raynaud phenomenon. The first case report is of a patient who was undergoing treatment of metastatic urothelial carcinoma of the bladder with gemcitabine, she developed scleroderma like changes after two cycles of gemcitabine. Cutaneous biopsy revealed diffuse sclerosis. Discontinuation of gemcitabine lead to partial reversibility of the fibrotic features[33]. The second case is of a woman with scleroderma who developed multiple ischemic digits after chemotherapywith gemcitabine[34].

## Radiation therapy

External neck irradiation may lead to radiation induced hypothyroidism. This can manifest as myalgia, joint stiffness and elevated creatine kinase. The effect is dose dependent with a gradual onset with many patients having subclinical hypothyroidism for several years before developing overt disease[35-36].

Xerostomia, may mimic the dry mouth of Sjogren's syndrome. Similarly, radiation therapy may trigger morphoea (localized scleroderma).

## Safety of radiation therapy in patients with rheumatologic disease

Several studies have suggested that patients with systemic sclerosis and systemic lupus erythematosus are at a greater risk of radiation toxicity[37-38]. However, a 2006 systematic review found methodologic shortcomings in most studies and failed to demonstrate that patients with rheumatologic diseases are at a greater risk of radiation related toxicity. Hence, radiation therapy is not contraindicated in patients with rheumatologic disease[39].

## Immune Checkpoint Inhibitor

Immune Checkpoint Inhibitors (ICI) are a type of cancer immunotherapy that work by blocking the negative regulation of T cells. They block inhibitory molecules on T cells, antigen presenting cells and tumours, thus allowing an enhanced endogenous T cell mediated immune response to cancer. Their effectiveness was first demonstrated in malignant melanoma in 2011 and since then they have been approved in management of various types of malignancies. Despite their important clinical benefits, ICIs are associated with a unique spectrum of adverse effects that are collectively termed as immune-related adverse events (irAEs). The irAEs occurs due to immune activation and increased inflammation by these drugs and can affect nearly every organ system[40]. The rheumatologic adverse effects include myositis, inflammatory arthritis, sicca syndrome and vasculitis[41]. Temporary immunosuppression with glucocorticoids or other immunosuppressive drugs like tumour necrosis factor-alpha antagonist and mycophenolate mofetil can be effective in management of most cases of irAEs[42]. The rheumatologic complications of ICI and their management will be discussed in detail separately.

## Conclusions

Malignancies have been associated with a number of rheumatic manifestations either of the illness itself or as paraneoplastic syndromes. Similarly various rheumatological diseases may occur as a result of treatment.

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