Agenda

A. Introduction
B. Paraneoplastic Rheumatic Syndromes
   a. Classification
      4. Vascular  5. Miscellaneous
   b. Practice Points
   c. Research Agenda
C. Malignancy Developing in a Pre-Existing CTD
D. Malignancy as a Complication of Therapy for Rheumatic Disorders
E. Direct Metastases to the Musculoskeletal System
F. Rheumatic Syndromes as a Complication of Therapy for Malignancy
A. Introduction

- There are a variety of ways in which musculoskeletal syndromes appear to be associated with malignancy.

- Certain rheumatic diseases have been associated with an increased risk of the subsequent development of malignancy.

- The converse situation also exists.

- Little is understood regarding the pathogenesis of CTD in association with neoplastic disease.
A. Introduction

- Many of the immunomodulatory agents may directly or indirectly be associated with an increased risk for the subsequent development of malignancy.

- Malignant neoplasms can be associated with a wide variety of paraneoplastic rheumatological syndromes.
B. Paraneoplastic Rheumatic Syndromes

- Paraneoplastic symptoms, unrelated to tumour mass or invasion, are present at diagnosis in about 10% of patients with cancer.
- Up to 50% experience a paraneoplastic syndrome at some time during the course of their illness.
- One-third of these are endocrine in nature, while the remainder are haematological, rheumatic and neuromuscular disorders.
- Among the paraneoplastic rheumatic syndromes, hypertrophic osteoarthropathy, carcinoma polyarthritis, myositis and vasculitis are the most frequently recognized.
- The disorders may coincide or follow the diagnosis of primary malignancy, but may precede the onset of cancer by as long as 2 years.
B. Paraneoplastic Rheumatic Syndromes

- The clinical course of a paraneoplastic musculoskeletal syndrome generally parallels that of the primary tumour.

- A paraneoplastic rheumatic syndrome can be suggested by a number of clinical features (following slide).

- The diagnosis can be made only after the cancer has been recognized and direct tumour invasion of bones, joints, peri-articular structures and muscles has been excluded.
Non-Metastatic Paraneoplastic Rheumatic Syndromes

Articular
- Hypertrophic osteoarthropathy
- Carcinoma polyarthritis
- Amyloid arthritis
- Secondary gout

Muscular
- Dermatomyositis and myositis
- Lambert-Eaton myasthenic syndrome

Cutaneous
- Palmar fasciitis and arthritis
- Panniculitis and arthritis
- Erythema nodosum
- Eosinophilic fasciitis
- Scleroderma-like syndromes
  - carcinoma of lung, breast, stomach
  - osteosclerotic myeloma (POEMS syndrome)
  - Werner's syndrome
Vascular
- Paraneoplastic vasculitis
- Wegener's granulomatosis
- Raynaud's syndrome and digital gangrene
- Erythromelalgia

Miscellaneous
- Reflex sympathetic dystrophy syndrome
- Jaccoud's arthropathy
- Lupus-like syndromes: with serositis, arthritis, antinuclear and antiphospholipid antibodies
- Relapsing polychondritis
- Multicentric reticulohistiocytosis
- Pyogenic arthritis (colonic carcinoma)
- Oncogenous osteomalacia
Common Features of Paraneoplastic Rheumatic Syndromes

- History of prior malignancy, exposure to carcinogens or family history of cancer
- Late age of onset >50 years
- Prominent constitutional symptoms: fever, malaise, weight loss
- A rapid onset of an unusual inflammatory arthritis, clubbing or periostitis, dermatomyositis, chronic unexplained cutaneous vasculitis, refractory Raynaud's syndrome or fasciitis, or Lambert-Eaton myasthenic syndrome
- A close temporal relationship between the onset of paraneoplastic symptoms and the discovery of the cancer
- Absence of metastases to the bones and joints
- Negative rheumatoid factor, culture results and synovial fluid crystal analysis
- Poor response to conventional medical treatment
- Improvement of symptoms with treatment of the underlying malignancy
- Re-appearance of the paraneoplastic symptoms with tumour recurrence
a. Classification
1. Articular

- **Hypertrophic osteoarthropathy**
  - Hypertrophic osteoarthropathy (HOA) is characterized by the clinical triad of oligo-or polyarthritis, clubbing of fingers and toes, and periostitis of the distal ends of long bones.
  - The arthritis, which often affects the knees, ankles, elbows, wrists, metacarpophalangeal (MCP) and proximal interphalangeal (PIP) joints, is the most frequent feature.
  - It is often symmetrical and painful.
  - It is sometimes associated with tenderness of the adjacent bones.
  - Synovial effusions are typically ‘non-inflammatory’ with a clear fluid of normal viscosity and a low leukocyte count with predominant lymphocytes and monocytes.
  - Clubbing is sometimes associated with a burning pain in the tips of fingers and toes.
  - Tenderness over the distal tibiae, radii and ulnae is commonly present.
  - The arthritis of HOA may predate the discovery of an underlying malignancy by several months.
1. Articular

-HOA occurs most frequently in patients with adenocarcinoma of the lung, affecting about 6 to 12% of patients.

-It is important to consider HOA in patients presenting with rapidly progressive clubbing of the fingers and toes, accompanied by severe joint and bone pains.

-Concerning lab studies, the ESR is often increased; in patients with widespread periostitis, serum alkaline phosphatase may be raised.

-Radiographs of the symptomatic sites may show symmetrical, bilateral periostitis of the distal long bones, presenting as linear ossification separated by a radiolucent zone from the underlying cortex (following figure).
1. Articular

- The most frequent sites are the tibiae, fibulae, radii, ulnae, femora and humeri.
- Scintigraphic abnormalities may precede the radiographic findings and include:
  
  increased radionuclide localization in the affected joints, parallel line periosteal uptake along the distal tibiae, fibulae, ulnae and radii (following figure), and occasional accumulation in the clubbed digits giving the digital tips a ‘string of lights’ appearance.

- The aetiology of HOA in patients with cancer is unknown.
- Radical cure of the underlying cancer often leads to rapid remission of HOA symptoms.
Figure 1. Hypertrophic osteoarthropathy in a patient with lung carcinoma. (A) Radiographs showing periostitis of distal tibiae and fibulae (arrows).
Figure 1. (B) Technetium-99M methylene diphosphonate scintiscan demonstrating increased parallel line uptake along the cortices of distal femora, tibiae and fibulae (‘tramline' sign).
1. Articular

- **Carcinoma polyarthriti**

  - Carcinoma polyarthritis is a seronegative inflammatory arthritis that may herald the onset of an occult malignancy.
  - Although its clinical presentation is variable, certain features suggest the possibility of an underlying malignancy, and serve to distinguish carcinoma polyarthritis from rheumatoid arthritis (RA).
  - These include:
    - a late age of onset of arthritis, an explosive onset,
    - asymmetric oligo- or polyarticular distribution,
    - predominant involvement of the joints of the lower extremities with frequent sparing of the wrists and joints of the hands,
    - and absence of erosions, deformities, rheumatoid factor, rheumatoid nodules or family history of RA.
1. Articular

- On rare occasions, the arthritis is symmetrical and may mimic rheumatoid arthritis.
- There is a close temporal relationship between the onset of carcinoma polyarthritis and detection of the tumour (about 10 months).
- Its prevalence is unknown.
- The arthritis, which typically occurs in women with carcinoma of the breast, or men with carcinoma of the lung, may antedate or follow the onset of the tumour.
- Synovial effusions are mildly inflammatory and the ESR is often elevated.
- There are no distinctive radiographic abnormalities.
- The pathogenesis of carcinoma polyarthritis is poorly understood.
- Frequent resolution of the arthritis following resection of the underlying neoplasm.
1. Articular

- **Amyloid arthritis**
  - Amyloid arthritis occurs most commonly in patients with multiple myeloma.
  - The arthritis which results from deposition of monoclonal light chains (AL amyloid) in the synovium, typically affects the shoulders, knees and wrists (following figure).
  - The arthritis is often symmetrical and relatively painless.
  - The `shoulder pad sign' is due to massive amyloid deposition with swelling of the glenohumeral joint.
1. Articular

-Synovial effusions are non-inflammatory with low total leukocyte counts.
- Spun synovial fluid sediment often contains `amyloid bodies': synovial villi containing amyloid deposits.
- Other clinical manifestations include peripheral neuropathy, carpal tunnel syndrome, peri-articular subcutaneous amyloid deposits, macroglossia, cardiomyopathy and nephropathy.
- The diagnosis of amyloid arthritis can be confirmed by bone marrow examination, serum and urine protein immunoelectrophoresis and biopsy of synovium, abdominal subcutaneous fat, or rectum.
- Management consists of treatment of multiple myeloma, and symptomatic treatment of the arthritis with analgesics or NSAIDs.
Figure 2. Subcutaneous amyloid and amyloid arthritis mimicking rheumatoid arthritis in a patient with multiple myeloma.
1. Articular

- **Secondary gout**
  - Hyperuricaemia and secondary gout may be associated with leukaemias, polycythaemia rubra vera, essential thrombocythaemia, lymphomas, myeloma, and rarely with carcinomas.
  - Chemotherapy of these disorders can lead to rapid cell lysis with severe hyperuricaemia, massive uricosuria, and acute obstructive nephropathy caused by uric acid crystals and stone formation (tumour lysis syndrome).
  - This can be prevented by adequate hydration and allopurinol therapy prior to cytotoxic therapy.
2. Muscular

- **Dermatomyositis and polymyositis**
  - Variety of non-metastatic muscular disorders including: generalized cachectic myopathy, proximal myopathy, dermatomyositis and polymyositis, and Lambert-Eaton myasthenic syndrome, may be associated with malignant neoplasms.
  - Several studies have demonstrated an increased incidence of cancer in patients with polymyositis (PM), or dermatomyositis (DM).
  - The risk is greatest in patients with DM, particularly within the first 3 years of diagnosis.
  - The frequency of cancer in patients with PM/DM has ranged from 6 to 60%.
2. Muscular

-Malignancies linked with PM/DM include carcinoma of lung, ovary, gastrointestinal tract, breast and testes, and less commonly lymphoma, leukaemia and melanoma.

-The exact relationship between cancer and myositis is not fully understood.

- In patients with DM, malignancy may develop prior to, concurrent with, or following the diagnosis of myositis.

-A higher mortality rate from cancer was also observed among patients with DM.

-The aetiology of myositis in patients with cancer is poorly understood.
2. Muscular

- Proposed mechanisms include:
  (a) a common environmental factor, such as a virus, a drug or a chemical, triggering both cancer and myositis in a genetically-predisposed host
  (b) an immune complex or cellular immune reaction involving tumour antigens cross-reacting with both muscle and skin antigens
  (c) tumour myotoxin or other products causing muscle and skin inflammation
  (d) both the tumour and myositis resulting from a subtle host abnormality of humoral and cellular immunity

- The clinical features of cancer-associated DM/PM are generally similar to those of idiopathic myositis.
2. Muscular

- Proximal muscle weakness is the principal presenting symptom.
- Serum creatine kinase (CK) levels are elevated in most but not all patients.
- Inflammatory arthritis occurs in about 50% of these patients and frequently affects the knees, elbows, wrists, MCP, PIP, and ankle joints.
- Cutaneous manifestations of cancer-associated DM include:
  - Heliotrope discoloration of the upper eyelids, peri-orbital oedema, malar rash, dry shiny erythematous skin over forehead,
  - Erythematous rash in a mantle distribution over light-exposed areas of anterior chest,
  - Gottron's papules over the dorsum of the MCP, and PIP joints, and peri-ungual telangiectases.
- Workup for the presence of malignancy should be undertaken.
- Workup should be tailored to the individual patient’s age, symptoms, and signs.
- Imaging of the chest, abdomen, and pelvis may increase the potential for discovery of underlying malignancy.
2. Muscular

- **Lambert-Eaton myasthenic syndrome**
  - This is a rare disorder of neuromuscular transmission, characterized by reduced release of acetylcholine from motor and cholinergic autonomic nerve terminals.
  - Antibodies against voltage-gated calcium channel epitopes, which disrupt calcium influx and reduce pre-synaptic release of acetylcholine from nerve terminals, are detectable in many patients.
  - The syndrome is characterized clinically by excessive fatiguability on exertion, hyporeflexia and proximal muscle weakness, especially in the lower extremities.
  - Other symptoms include diplopia, ptosis, dysarthria and orthostatic hypotension.
2. Muscular

- Lambert-Eaton syndrome is associated with small-cell lung carcinoma in 60% of patients.
- The tumour is usually discovered within 1 to 2 years of the onset of muscle weakness.
- Antibodies directed against small-cell carcinoma cell membranes are thought to cross-react with neuronal calcium channels.
- Improvement of the symptoms may follow eradication of the tumour.
3. Cutaneous Paraneoplastic Rheumtic Syndromes

- **Paraneoplastic palmar fasciitis-polyarthritis syndrome**
  - This has been described in association with ovarian and non-ovarian malignancy.
  - Clinical manifestations include thickening of the palmar fascia and an inflammatory symmetrical arthritis commonly affecting knees, ankles, elbows and wrists.
  - The arthritis is often refractory to NSAIDs and corticosteroids, but may improve following treatment of the primary tumour.
  - An immune pathogenesis is suggested by the frequent presence of antinuclear antibodies in the serum, and of immune deposits in palmar fascial biopsies.
3. Cutaneous Paraneoplastic Rheumatic Syndromes

- **Paraneoplastic panniculitis-arthritis syndrome**
  
  - A liquefying panniculitis, with subcutaneous tender nodules and an inflammatory mono- or polyarticular arthritis, may be the presenting symptoms of carcinoma of the pancreas.
  
  - The skin lesions, which appear as tender red subcutaneous nodules on the legs, thighs and buttocks, may later liquefy, draining a sterile yellowish material containing globules of fat.
  
  - The syndrome has also been described in patients with acute pancreatitis.
  
  - It is thought to result from release into the circulation of pancreatic lipase causing fat necrosis, and secondary inflammation of both the subcutaneous tissue (panniculitis) and synovium (arthritis).
3. Cutaneous Paraneoplastic Rheumatic Syndromes

- The possibility of pancreatic cancer should be considered in older men presenting with unexplained arthritis and tender subcutaneous nodules.

- Hematologic malignancies are most often associated with this syndrome.

- The diagnosis can be confirmed by abdominal CT, biopsy of a skin nodule and serum lipase determination.

- Eosinophilia is more common in patients with cancer-associated panniculitis than in those with acute pancreatitis.

- Symptoms may improve after treatment of pancreatic carcinoma.
3. Cutaneous Paraneoplastic Rheumatic Syndromes

- **Paraneoplastic Eosinophilic fasciitis**
  - Diffuse fasciitis of the extremities and trunk, associated with joint contractures, eosinophilia, hypergammaglobulinaemia and raised ESR.
  - It has been reported in patients with myeloproliferative and lymphoproliferative malignancies.
  - An association between familial eosinophilic fasciitis and breast carcinoma has also been described.
  - The pathogenesis of malignancy-associated eosinophilic fasciitis is unknown.
  - Immune mechanisms and cytokines released from the neoplastic cells have been implicated.
  - Cancer-associated fasciitis occurs most commonly in women.
  - It is often unresponsive to corticosteroid therapy but may regress with successful treatment of the underlying malignancy.
3. Cutaneous Paraneoplastic Rheumatic Syndromes

- **Paraneoplastic scleroderma-like syndromes**

  - Skin changes resembling scleroderma may occur in patients with carcinoma of the stomach, breast or lung, metastatic melanoma, and osteosclerotic localized myeloma.
  
  - POEMS syndrome is a rare form of plasma cell dyscrasia.
  
  - It is usually a localized osteosclerotic myeloma, associated with polyneuropathy, organomegaly, endocrinopathy, monoclonal protein and skin changes suggestive of scleroderma.
4. Paraneoplastic Vascular Syndromes

- **Paraneoplastic vasculitis**
  - Paraneoplastic necrotizing vasculitis may occur in association with myeloproliferative and lymphoproliferative disorders, myelodysplastic syndrome, and less frequently, malignant melanoma and carcinoma of the lung, prostate, colon, breast and ovary.
  - It often develops after the diagnosis of cancer is established but may antedate the discovery of the malignancy, or herald its recurrence.
  - The frequency of an underlying malignancy in patients with leukocytoclastic vasculitis is estimated to be 4.2%.
  - Small-vessel cutaneous leukocytoclastic vasculitis is the most common manifestation of cancer-associated vasculitis.
  - A vasculitis of medium-sized vessels, resembling polyarteritis nodosa, may occur in association with hairy cell leukemia (HCL).
4. Paraneoplastic Vascular Syndromes

- Clinical manifestations include fever, cutaneous vasculitis, myalgia, arthritis, acute abdomen due to mesenteric vasculitis, coronary arteritis and mononeuritis multiplex with footdrop.

- The aetiology of cancer-associated vasculitis is unknown.

- Suggested mechanisms include:
  1. Vascular inflammation induced by immune complexes involving tumour antigens
  2. Vascular injury by antibodies cross-reactive to both tumour and endothelial cells
  3. In the case of HCL, direct vascular damage by hairy cells infiltrating the arterial wall

- A close temporal relationship between renal cell carcinoma and Wegner’s granulomatosis has been reported.
Paraneoplastic Raynaud’s syndrome and Digital necrosis

-Raynaud's phenomenon, presenting in individuals 50 years of age or older, has been reported in association with carcinoma of the lung, ovary, small bowel, breast, pancreas or kidney, lymphoma, leukaemia and myeloma.

-It may antedate the discovery of malignant neoplasm by several months.

- Progression to digital gangrene occurs in about 80% of patients, and asymmetric involvement of the digits is reported in 30% of patients.

-The aetiology of Raynaud's phenomenon in patients with a cancer is poorly understood, but paraproteins, cryoglobulins and cytokines have been implicated.
4. Paraneoplastic Vascular Syndromes

- The vasospastic disorder is often refractory to both vasodilator therapy and sympathectomy, but may regress with radical treatment of the tumour.

- Digital ischaemia with pulp atrophy, pitted scars and overt digital gangrene, is an unusual manifestation of carcinoma of the lung, small bowel, kidney or other malignancy.

- Mechanisms implicated in its pathogenesis include:
  (1) cancer-associated arterial vasospasm, (2) vascular occlusions secondary to a hypercoagulable state, and (3) a paraneoplastic necrotizing vasculitis.
4. Paraneoplastic Vascular Syndromes

- **Paraneoplastic erythromelalgia**

  Erythromelalgia is characterized by attacks of severe burning pain, erythema, and warmth of the feet and less commonly the hands, without evidence of arterial occlusion.

  Symptoms are often provoked by exposure to heat, exercise and dependency.

  There are two forms of erythromelalgia: an idiopathic primary form (60%), and a secondary form (40%).

  About 20% of patients with the secondary form have an underlying myeloproliferative disorder, such as polycythaemia rubra vera and essential thrombocythaemia.

  Symptoms of erythromelalgia may antedate the onset of malignancy by months or years, and it is important that these patients be monitored with periodic blood cell counts.

  Management includes aspirin 325 to 650 mg daily, and treatment of the underlying haematological malignancy.
5. Miscellaneous Paraneoplastic Rheumatic Disorders

*Cryoglobulinemia*

- Cryoglobulinemia can be characterized by hyperviscosity symptoms or by vasculitis.
- 5 to 8% of patients with mixed cryoglobulinemia may go on to develop non-Hodgkin’s lymphoma after 5 to 10 years of cryoglobulinemia.

*Antiphospholipid antibodies*

- Presence of these antibodies in patients with both solid tumors and lymphoproliferative disorders is at a higher frequency than the general population.
5. Miscellaneous Paraneoplastic Rheumatic Disorders

- Paraneoplastic reflex sympathetic dystrophy syndrome (RSDS)
  - RSDS has rarely been reported in association with carcinoma of the lung, colon, pancreas and ovary, and chronic myeloid leukaemia.
  - It is characterized by diffuse burning pain, allodynia, swelling and impaired function of an extremity, associated with vasomotor, sudomotor and dystrophic skin changes.
  - The pathogenesis of cancer-associated RSDS is unknown.
Paraneoplastic Jaccoud-type arthropathy

- Jaccoud's arthropathy is a relatively painless, non-erosive but deforming arthropathy predominantly affecting the hand joints.
- It is typically associated with reducible ulnar deviation and flexion deformities of the MCP, and sometimes swan-neck deformities of fingers.
- Jaccoud-type arthropathy occurs most frequently in patients with SLE, and has also been reported as a manifestation of carcinoma of the lung.
5. Miscellaneous Paraneoplastic Rheumatic Disorders

- **Paraneoplastic lupus-like syndromes**
  - Lupus-like syndromes have been described in association with various primary or recurrent malignancies.
  - Malignancies can be Hodgkin's disease, myelodysplastic syndromes, thymoma and carcinoma of the lung, breast or ovary.
  - Clinical manifestations may include pleural effusions, pneumonitis, or pericarditis.

- **Oncogenous osteomalacia**
  - Tumour-induced osteomalacia is a rare syndrome characterized by hypophosphataemia, hyperphosphaturia, low plasma 1,25-dihydroxy vitamin D3 concentrations and osteomalacia.
  - The clinical course is often protracted, and symptoms include diffuse bone pains, proximal muscle weakness and spontaneous fractures.
5. Miscellaneous Paraneoplastic Rheumatic Disorders

- **Paraneoplastic multicentric reticulohistiocytosis**
  - Multicentric reticulohistiocytosis (MRH) is characterized by a deforming destructive symmetrical arthritis, usually of the hands, associated with subcutaneous nodular lesions.
  - Two observations suggest that MRH may represent a paraneoplastic disorder:
    1. (a) occurrence of malignancy in about a third of patients with MRH, antedating the detection of cancer in 75% of these patients
    2. (b) frequent regression of MRH after successful treatment of the malignancy

- **Paraneoplastic relapsing polychondritis**
  - A few cases of relapsing polychondritis with features of a paraneoplastic syndrome have been described in association with leukaemia, lymphomas, and myelodysplastic syndrome.
Paraneoplastic polymyalgia rheumatica and giant-cell arteritis

- Although patients with polymyalgia rheumatica (PMR) do not appear to be particularly susceptible to malignant disease, haematological malignancies and a variety of primary and metastatic solid tumours may present with a syndrome resembling PMR.

- The relationship between PMR and malignancy is questionable.

- Both conditions may share a number of common features: older age of onset, diffuse myalgia, weight loss, malaise and an elevated ESR.

- Cancer-associated PMR often responds poorly to low-dose corticosteroid therapy but may regress with eradication of the underlying malignancy.

- Malignancies occur in patients with giant-cell arteritis (GCA) at rates comparable to those in the general population.
A number of diverse non-metastatic paraneoplastic rheumatic disorders may occur in patients with cancer. While hypertrophic osteoarthropathy, carcinoma polyarthritis, dermatomyositis and paraneoplastic vasculitis are well recognized, others, such as fasciitis, panniculitis, erythema nodosum, Raynaud's syndrome, digital gangrene and lupus-like syndromes, are less known. They may occasionally be the presenting manifestation of a hidden malignancy.

Clinical clues suggesting a paraneoplastic rheumatic syndrome include:
- a rapid onset of an unusual inflammatory arthritis,
- clubbing or diffuse bone pains in a patient 50 years of age or older,
- rapidly progressive dermatomyositis, chronic unexplained cutaneous vasculitis, refractory fasciitis, Raynaud's phenomenon or digital gangrene, and Lambert–Eaton myasthenic syndrome.

Treatment of the underlying neoplasm usually, but not invariably, results in regression of paraneoplastic rheumatic manifestations.
c. Research Agenda

- Substantial evidence points to an aetiological relationship between cancer and paraneoplastic rheumatic syndromes.
- The exact nature of the association is not fully understood.
- Research into the intricate interrelationship between malignant neoplasms and paraneoplastic rheumatic manifestations may shed some light on:
  - immunogenetic or other pathogenetic mechanisms underlying these disorders.
- This will provide an impetus to explore potentially curative treatment modalities.
C. Malignancy Developing in a Pre-Existing CTD

- Autoimmune rheumatic diseases and lymphocytic malignancies are related and this association is bidirectional.

- Lymphomas occur more frequently in the course of autoimmune diseases and autoimmune rheumatic manifestations occur in the course of lymphocytic malignancies.

- An increased incidence of malignant lymphocytic diseases is present in patients with rheumatoid arthritis, systemic lupus erythematosus, Sjogren’s syndrome, and autoimmune thyroid disease.

- Descriptions of lymphocytic malignancies among other autoimmune rheumatic diseases have been published.

- In some patients, the malignant disease is diagnosed months or years before the appearance of the rheumatic disease.
Malignancy Developing in a Pre-Existing Connective Tissue Disease

- Sjögren's syndrome (lymphoma)
- Systemic lupus erythematosus (lymphoma)
- Discoid lupus erythematosus (squamous-cell epithelioma)
- Rheumatoid arthritis (lymphoma, myeloma)
- Scleroderma (lung, oesophageal, and ? breast carcinoma)
- Eosinophilic fasciitis (haematological malignancy)
- Lymphoid granulomatosis (lymphoma)
C. Malignancy Developing in a Pre-existing CTD

- **Sjogren’s syndrome**
  - Primary Sjogren’s syndrome has been shown to be associated with an increased risk of lymphoproliferative diseases, the highest incidence among the autoimmune diseases.
  - The onset of the lymphoma may be preceded by angioimmunoblastic lymphadenopathy or pseudolymphoma.
  - Sjogren’s syndrome is considered a link between autoimmune and lymphoproliferative diseases.
  - Presence of a viral trigger may account for malignant transformation.
  - Chromosomal translocation may correlate with the development of lymphoma.
C. Malignancy Developing in a Pre-existing CTD

- **Rheumatoid Arthritis**
  - Presence of RA appears to convey an increased risk for development of lymphoproliferative disorders
  - Associated factors:
    - presence of paraproteinemia,
    - greater disease severity,
    - longer disease duration,
    - and immunosuppression
  - Clinical alert:
    - rapidly progressive, refractory flare in long-standing rheumatoid disease may suggest an underlying malignancy
D. Malignancy as a Complication of Therapy for Rheumatic Disorders

**Immunosuppressive therapy**
- Cyclophosphamide (SLE, Wegener's granulomatosis): haematological malignancies, carcinoma of the bladder
- Azathioprine (RA): lymphoma
- Methotrexate (RA): lymphoma
- Cyclosporin: lymphoma, skin malignancies

**Radiation therapy**
- Radiation for ankylosing spondylitis: leukaemia, basal cell carcinoma
- Total lymphoid irradiation for RA: myeloproliferative disorders
E. Direct Metastases to the Musculoskeletal System

- Skeletal metastases and metastatic carcinomatous arthritis
- Joint manifestations of leukaemia: leukaemic synovitis, haemarthrosis, gouty arthritis
- Joint manifestations of lymphoma: lymphomatous arthritis, gouty arthritis
- Synovial reaction to juxta-articular bony or capsular carcinomatous, leukaemic, or lymphomatous lesions
F. Rheumatic Syndromes as a Complication of Therapy for Malignancy

- Gouty arthritis: cytotoxics, vinblastine, cyclosporin
- Raynaud's syndrome: bleomycin, cisplatin
- Vasculitis: tamoxifen, intrahepatic chemotherapy
- Hand-foot syndrome: 5-fluorouracil
- Arthralgias/arthritis
  - adjuvant therapy for breast carcinoma
  - interleukin-2, and interferon-a therapies
  - intravesical BCG for bladder carcinoma
References

- Uptodate version 12.2
Thank You