Malignancy and Rheumatic Disease

Joanne Valeriano, MD

Malignancy and rheumatologic diseases are interrelated in multiple ways.

Introduction

The association between malignancy and musculoskeletal or rheumatic disease is complex and intriguing. The musculoskeletal system may be either directly or indirectly associated with cancer, or paraneoplastic syndrome and malignancy may arise in preexisting rheumatic disease. In addition, treatment of rheumatic disease with immunosuppressants may result in malignancy and, conversely, chemotherapeutic treatment of the malignancy may result in rheumatic syndromes. Investigation of the intricate interrelationships of these diseases may enhance our understanding of their etiologies and thus lead to better control.

Metastases to the Musculoskeletal System

Arthritis resulting from metastatic carcinoma is rare. It usually results from juxta-articular bone involvement rather than direct involvement of the synovium. A 1980 review of the literature summarized 19 case reports of arthritis resulting from metastatic carcinoma, and the majority were due to breast cancer, lung cancer, and melanoma. The features that suggest this diagnosis are listed in Table 1. Other presentations may include phalangeal metastases mimicking the acute synovitis of gout, osteomyelitis, tenosynovitis, acroosteolysis, or a symmetric, rheumatoid-like arthritis. Due to the patchy synovial involvement by tumor, synovial biopsy is rarely helpful, although synovial fluid cytology may be diagnostic.

Musculoskeletal Manifestations of Leukemia and Lymphoma

The musculoskeletal manifestations of leukemia include symmetric or migratory polyarthritis or arthralgias, bone pain and tenderness, and back pain mimicking a radiculopathy secondary to meningeal involvement. Approximately 4% of adults with leukemia have articular manifestations, and approximately 14% of children and, in some series, 13.5% of patients overall have artricular symptoms as presenting features of leukemia. Leukemic synovitis may be the initial manifestation of relapse, even if not present at the time of initial diagnosis of leukemia. Leukemic joint manifestations may be the result of leukemic synovial infiltration, hemorrhage into the joint or periarticular structures, crystal-induced synovitis, or synovial reaction to adjacent bony, periosteal or capsular lesions. The features of leukemic arthritis are presented in Table 2. Synovial effusions are usually mildly inflammatory and rarely reveal leukemic cells. Use of a technique involving immunofluorescence and a panel of early B-cell and myeloid antigens may increase the yield of identifying leukemic cells in synovial effusion and biopsy. Radiographic abnormalities include metaphyseal rarefaction and osteolytic or periosteal reaction. Treatment of the underlying leukemia may relieve bone and joint symptoms and may indicate efficacy of the therapy for leukemia. Adjunctive radiation therapy to affected joints may be necessary to control symptoms.
Musculoskeletal manifestations of lymphoma include bone pain, which is the most common, as well as monarthritis, polyarthritis, and spinal cord involvement. Cutaneous T-cell lymphoma may present with a chronic nonerosive polyarthritis.  

The clinical features and associated malignancies of selected musculoskeletal or rheumatic paraneoplastic syndromes are presented in Table 3.

<table>
<thead>
<tr>
<th>Paraneoplastic Syndrome</th>
<th>Clinical Features</th>
<th>Most Common Associated Malignancy</th>
<th>Laboratory Values</th>
<th>Other</th>
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<tbody>
<tr>
<td>Dermatomyositis and polymyositis</td>
<td>Gradually progressive proximal muscle weakness, rash with dermatomyositis</td>
<td>Same as the most common overall based on the age and sex of the patient</td>
<td>Increased muscle enzymes (increased creatine phosphokinase)</td>
<td>Abnormal electromyography</td>
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<td>Muscle biopsy: muscle fiber necrosis with minimal inflammation</td>
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<td>Myasthenic syndrome (Life-Lambert)</td>
<td>Muscle weakness (most prominent in the paravertebral region, especially the neck and shoulder girdle and limb girdle muscles, particularly the paravertebral muscles, and the diaphragm), difficulty with rapid eye movements, areflexia, and weakness of the muscles of the jaws or facial muscles</td>
<td>Small-cell lung cancer</td>
<td>Electromyography: increased muscle action potential with normal nerve stimulation of axons &gt;10 m/s</td>
<td>Poor response to edrophonium</td>
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<td>Synovial fluid: noninflammatory, predominantly lymphocytes and monocytes</td>
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<td>Hydrorhaphic pulmonary edema-erythroderma</td>
<td>Clubbing fingers and toes, periungual telangiectasia, skin rash resembling teardrop dermatitis, and skin nodules</td>
<td>Lung adenocarcinoma, also bronchioloalveolar carcinoma, inflammatory myofibroblastic tumors</td>
<td>Serum levels: increased alkaline phosphatase and osteoclast-like cell activity</td>
<td>Poor response to chemotherapy</td>
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<td>Increased uptake on radionuclide bone scan</td>
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<td>Cardiomyopathy polycythemia</td>
<td>Asymptomatic (predominantly nonextreme activities); absent rhabdomyolysis</td>
<td>Breast cancer in women; no predominate malignancy reported in men</td>
<td>Serology: negative ANA, negative rheumatoid factor</td>
<td>No distinctive radiographic features</td>
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<td>Amyloidosis</td>
<td>Neurocranium (peripheral edema), cutaneous (itchy papules), macroglossia, subcutaneous nodules, subcutaneous crepitus, skin thickening, involvement of the ears, and carpal tunnel syndrome; carciinomyopathy-pseudotumoral</td>
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<td>Biopsy of infiltrated tissue with Congo red stain (fibrillary, emerald green birefringence)</td>
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<td>Lupus-like syndrome</td>
<td>Raynaud's phenomenon, pleuritic effusions, pneumonitis, pericarditis, nondeforming polyarthritis</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td>Ovarian adenocarcinoma, lymphoma, thymoma, myasthenia gravis, lung, colon, and breast cancer</td>
</tr>
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<td></td>
<td></td>
<td></td>
<td></td>
<td>Serology: positive ANA</td>
</tr>
<tr>
<td>Reflex sympathetic dystrophy</td>
<td>Type I (neurogenic pain syndrome)</td>
<td>Type II (pallor, paresthesia, polyarthritis)</td>
<td>Type I: brain, lung, bladder, uterus, breast, and gastrointestinal; Type II: ovarian cancer, small-cell lung cancer, adenocarcinoma of the pancreas, chronic myelogenous leukemia, and Hodgkin's lymphoma</td>
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<td>Radiographic osteopenia of affected extremities in Type I and II; radiodense bone scan may show increased uptake in affected extremities (Types I and II)</td>
</tr>
</tbody>
</table>

**Musculoskeletal or Rheumatic Paraneoplastic Syndromes**

Paraneoplastic syndromes include myopathy, arthropathy, and miscellaneous presentations. Separate criteria to define the paraneoplastic rheumatic syndromes do not exist; however, certain features may suggest an underlying neoplastic process.

Approximately 15% of hospitalized patients with a malignancy have a paraneoplastic syndrome. One third of the cases are endocrine related, and the remainder are hematologic, rheumatologic, and neuromuscular disorders. The risk that a patient with cancer will develop a paraneoplastic syndrome is 50% to 75%.

**Dermatomyositis and Polymyositis**

The facial rash of dermatomyositis includes heliotrope discoloration of the upper eyelids and periorbital edema (Fig 1A). Gottron's papules, which are usually located over the metacarpophalangeal and proximal interphalangeal joints, may range from erythematous, purplish, flat papules to reddish-white, shiny, slightly scaly, atrophic lesions (Fig 1B). Additionally, an erythematous eruption may appear in a mantle distribution over light-exposed areas (Fig 1C).
The relationship between myositis and malignancy is unclear, and reports in the literature are conflicting. Malignancy may develop prior to, concurrently with, or following the onset of myositis. In most cases, the relationship is temporal, with one entity having developed within one year of the other. In a Swedish population-based study, the relative risk of cancer in patients with polymyositis and those with dermatomyositis was 1.75 and 2.9, respectively, compared with the normal population. The association is most striking in men older than 50 years of age -- more than 70% of this population have developed cancer. Malignancy is not generally associated with childhood dermatomyositis or polymyositis, but it occasionally occurs.

**Eaton-Lambert Myasthenic Syndrome**

With the accumulating evidence that myasthenic syndrome is an autoimmune condition and with its presentation of muscle weakness, it is included in this section. Most patients with this Eaton-Lambert myasthenic syndrome have lung cancer, particularly small-cell lung cancer. Lambert and associates reported that this syndrome is found in 6% of patients with small-cell lung cancer and in less than 1% of all lung cancer patients.

**Arthropathy**

Hypertrophic pulmonary osteoarthropathy (HPO) is classified as primary or secondary. Malignancy is among the underlying causes of secondary HPO. The syndrome includes clubbing of the fingers and toes, periostitis of the long bones, and oligosynovitis or polynovitis. Patients often appear with arthralgias or arthritis rather than clubbing, and HPO should be considered in adult patients with this presentation. Rapid progression of clubbing accompanied by fairly severe joint and bone pain should raise the suspicion of a paraneoplastic process. HPO is found most frequently in patients with lung cancer and occurs in 12% of patients with adenocarcinomas. It is almost nonexistent in patients with small-cell lung cancer. The HPO syndrome often occurs with mesothelioma and the rare neurilemmomas of the diaphragm. Metastases from renal cancer, thymoma, leiomyoma of the esophagus, intrathoracic Hodgkin’s disease, osteogenic sarcoma, fibrosarcoma, and undifferentiated nasopharyngeal tumors have also been associated with HPO.

The diagnosis of HPO is based on physical findings and radiographs that demonstrate periostitis of the distal long bones (Fig 2), osteophytosis and tufting of terminal processes in the hands, and occasionally acroosteolysis. Radionuclide bone scan abnormalities may precede radiographic changes. Ablation or cure of the underlying malignancy may lead to remission of symptoms within hours to days, and radiographic abnormalities may resolve within weeks to months.
Carcinoma Polyarthritis

Polyarthritis may be the presenting feature of solid tumors. The development of a paraneoplastic arthritic syndrome should be considered patients over 55 years of age with a more explosive presentation of an asymmetric, predominantly lower-extremity arthritis. No predominant malignancy has been reported in men with paraneoplastic arthritic syndrome, but 80% of women with this syndrome have had breast cancer. Mechanisms that have been postulated to explain carcinomatous polyarthritis include (1) immune complexes that cause synovitis, (2) tumor-generated mediators that provoke a connective tissue reaction, (3) host factors in reaction to the tumor that damage natural barriers, thus allowing evolution of connective tissue disease, and (4) a common host defect that results in the expression of both neoplasia and connective tissue disease.

Amyloidosis

Fifteen percent of amyloidosis cases occur with malignant diseases that include multiple myeloma, lymphomas, and carcinomas. Amyloidosis develops in 6% to 15% of patients with multiple myeloma and Waldenström's macroglobulinemia, in 4% of patients with Hodgkin's disease, and in 1% of patients with other lymphomas. Carcinomas that are associated with amyloidosis include hypernephromas and cancers of the bladder, renal pelvis, uterine cervix, and biliary tract. Amyloidosis can be caused by monoclonal light chains (AL) or other proteins (AA). The clinical spectrum of amyloidosis of malignancy includes peripheral and autonomic neuropathy, weight loss, and restrictive cardiomyopathy. Cutaneous manifestations include pinch purpura, macrogllosia, subcutaneous nodules, and "scleroderma-like" skin infiltration. Arthropathy results from amyloid infiltration and involves large joints, and it commonly causes a painless limitation of motion in wrists, knees, and shoulders. The "shoulder-pad sign" may develop with massive infiltration of the glenohumeral articulation. Carpal tunnel infiltration may lead to carpal tunnel syndrome.

Jaccoud's Arthropathy

Jaccoud's arthropathy is a rapidly progressive, nonerosive, painless arthropathy resulting in reducible deformities that predominantly involve the small joints of the upper extremities. Initially described in rheumatic fever, it has been reported as an initial manifestation of carcinoma of the lung. The most common cause of Jaccoud's arthropathy is systemic lupus erythematosus.

Miscellaneous Rheumatic or Musculoskeletal Syndromes

Lupus-like Syndromes

Lupus-like syndromes have been associated with various malignancies such as Hodgkin's disease, myeloma, and tumors of the lung, colon, breast, ovaries, and testes. Clinical features include pleural effusions, pneumonitis, pericarditis, nondeforming polyarthritis, and/or positive antinuclear antibodies. The syndromes may occur with the primary malignancy or with occult recurrences. A syndrome of rapidly progressive Raynaud's phenomenon and serositis has been reported in association with ovarian adenocarcinoma. The antinuclear antibodies did not appear to be directed against the common nonnucleolar antigens seen in native systemic lupus erythematosus, which supports a causal, true paraneoplastic relationship.

Necrotizing Vasculitis

Necrotizing vasculitis is most often associated with leukemia and lymphomas. The most common manifestation is cutaneous vasculitis due to small vessel involvement. Involvement of medium-sized vessels may cause a periarteritis nodosa-type of vasculitis (eg, hairy-cell leukemia). Manifestations may then include acute abdomen and mononeuritis multiplex. In a report of 11 cases and a review of 46 cases by Sanchez-Guerrero et al, hematologic malignancies were found in 34 patients, and solid tumors were present in 12 patients.

Digital Gangrene

Malignancy must be considered in the differential diagnosis of digital gangrene. Patients may present with a range of findings that include splinter hemorrhages, pulp atrophy, and digital gangrene. Possible mechanisms include cryoglobulinemia, immune complex-induced vasospasm, a hypercoagulable state, marantic endocarditis with emboli, and necrotizing vasculitis.

Reflex Sympathetic Dystrophy

Reflex sympathetic dystrophy is a nonsegmental pain syndrome involving one or more extremities combined with trophic skin changes, vasomotor instability, and radiographic evidence of osteopenia. The pathophysiology is unknown; however, it has been associated with a number of conditions including various types of malignancy. There are two types of reflex sympathetic dystrophy: -- the more common shoulder-hand syndrome (Type I), which may result from direct tumor involvement of an extremity, and the more aggressive palmar fasciitis and polyarthritis syndrome (Type II), which occurs more commonly in ovarian carcinoma. Patients present with pain and limited motion of the hands and shoulders, as well as polyarthritis and a deforming palmar fasciitis. Deposits of immunoglobulin G have been found in palmar fascia, suggesting an immunopathologic mechanism.

Scleroderma

The definition of scleroderma as a paraneoplastic syndrome is controversial. In an analysis of patients with coexisting scleroderma and malignancy, two major tumor types -- adenocarcinoma and carcinoid -- were found. Although all patients had cutaneous manifestations of scleroderma, fewer than half had proven systemic sclerosis.

There are two syndromes in which patients may present with skin changes suggestive of scleroderma -- POEMS and Werner's syndrome. POEMS is a rare form of plasma cell dyscrasia with polyneuropathy, organomegaly, endocrinopathy, monoclonal protein, and skin changes suggestive of scleroderma. Werner's syndrome is a rare, autosomal, recessive connective-tissue disorder characterized by juvenile cataracts, scleroderma-like skin changes, accelerated aging, and a high incidence of...
neoplasms of connective-tissue origin. A diagnosis of POEMS syndrome or Werner's syndrome should alert the physician to the possibility of underlying malignancy.

**Erythema Nodosum**

Erythema nodosum is a panniculitis syndrome in which the lesions have a characteristic appearance of nodules or plaques with erythematous, smooth, shiny overlying skin. The lesions are extremely tender and can be seen in Hodgkin's and non-Hodgkin's lymphoma and leukemia. Histologically, the lesions may be true erythema nodosum or lymphomatous lesions. Pancreatic carcinoma may also present with panniculitis and arthritis due to fat necrosis by the pancreatic enzymes.

**Pyogenic Arthritis**

An underlying colonic neoplasm should be considered when a patient presents with a pyogenic arthritis due to an unusual enteric pathogen. Pyogenic arthritis is usually a late complication of colon cancer but rarely is a presenting manifestation.

**Erythromelalgia**

Erythromelalgia is characterized by attacks of severe burning and painful erythema, as well as warmth of the hands and, more prominently, the feet. The syndrome may be primary (59%) and secondary (41%) and 20% of patients have underlying myeloproliferative syndromes. The symptoms may precede the development of the malignancy by a median of 2.5 years, thus routine monitoring for the development of hematologic malignancy in such patients seems reasonable.

**Tumor-Induced Osteomalacia**

Tumor-induced osteomalacia is a rare syndrome characterized by hypophosphatemia, hyperphosphaturia, low plasma 1,25-dehydroxyvitamin D, and osteomalacia. All biochemical and pathologic abnormalities disappear when the tumor is removed. A possible etiology includes a hormonal factor elaborated by tumor cells that inhibits phosphate transport in renal epithelial cells.

**Malignancy in Preexisting Connective Tissue Disease**

An increased incidence of malignancy has been reported in almost all connective tissue diseases (CTDs). Several possibilities may explain the increase: (1) therapy for the CTD provokes the malignancy, (2) environmental factors lead to malignancy and CTD, (3) specific HLAs or an immunologic disorder lead to malignancy and CTD, and (4) tissue alteration by the CTD leads to subsequent malignant transformation.

**Systemic Lupus Erythematosus**

Systemic lupus erythematosus (SLE) is associated with increased malignancy, with lymphoma being the most common. Recognition of this association is important since lymphoma can mimic an exacerbation of SLE with adenopathy, fever, malaise, and splenomegaly. Further treatment with corticosteroids may mask the diagnosis of lymphoma.

**Sjögren's Syndrome**

Sjögren's syndrome is characterized by dry eyes and mouth. It is a chronic inflammatory process of exocrine glands and may be primary or secondary to another CTD. Patients with Sjögren's syndrome have a 40-fold increased risk of lymphoma. B-cell lymphoma is the most common malignancy, but T-cell lymphoma has also been reported. Patients may develop pseudolymphoma, a malignant extraglandular extension of lymphoproliferation. Pseudolymphoma may either regress or progress to neoplasia, including lymphoma or macroglobulinemia. Indications of the progression to lymphoma include a decrease in serum immunoglobulin M, the disappearance of lymphoma can mimic an exacerbation of SLE with adenopathy, fever, malaise, and splenomegaly. Further treatment with corticosteroids may mask the diagnosis of lymphoma.

**Rheumatoid Arthritis**

The increased risk of lymphoproliferative malignancy in rheumatoid arthritis (RA) appears to be independent of cytotoxic therapy. A large population-based study in Finland in 1982 demonstrated an increased incidence of Hodgkin's disease, non-Hodgkin's lymphoma, myeloma, and leukemia in RA patients. The development of lymphoma appears to be related to the duration rather than to the severity of RA. The mean interval from the onset of RA to the development of malignancy is 17 years. The initial association of myeloma with RA was proposed in 1955. In 1991, Kelly et al prospectively evaluated 23 patients with RA and a paraprotein. The paraprotein was monoclonal in 21 patients and biclonal in two patients. After a median follow-up of four years after the diagnosis of a paraprotein, five patients developed myeloma. Of these, three had an immunoglobulin-A paraprotein. The remaining two patients, both of whom had secondary Sjögren's syndrome, developed non-Hodgkin's lymphoma. Although the prevalence of a monoclonal protein in patients with RA is not significantly higher than that in the general population, there is a higher proportion of immunoglobulin A and a greater risk of malignant transformation.

**Progressive Systemic Scleroderma**

Alveolar cell carcinoma comprises 50% of lung tumors in progressive systemic scleroderma (PSS) compared with a general incidence of less than 4% of all primary lung tumors. This difference is believed to be the result of metaplasia superimposed on fibrosis rather than a direct consequence of PSS. Two case studies reveal the onset of breast cancer at or near the onset of scleroderma. Barrett's metaplasia and adenocarcinoma of the esophagus have also been reported to occur in PSS.

**Chemotherapy-Induced Rheumatic Syndromes**

**Gout**

Cytotoxic drug therapy for malignancy -- particularly for lymphomas and related lymphoproliferative diseases -- results in the massive release of nucleic acids from killed tumor cells as well as the formation of large amounts of uric acid that can cause acute gouty arthritis. The use of cyclosporin following bone marrow transplantation may also result in acute gouty arthritis, as well as elevated serum uric acid concentration and tophaceous deposition.

**Raynaud's Phenomenon**
Raynaud's phenomenon occurs in approximately 40% of men treated with a cisplatin-based combination chemotherapy for testicular cancer.\textsuperscript{51} Although it is unclear which drug used to treat testicular cancer causes this toxicity, bleomycin is the most likely because it can cause Raynaud's phenomenon when used alone.\textsuperscript{52} Clinically, patients present with painful digits. Paresthesia develops at a mean of 10 months following the start of chemotherapy and lasts five or more years. The mechanism appears to be a vasomotor phenomenon due to impaired smooth muscle function in the terminal arterioles without evidence of obstruction.\textsuperscript{53}

### Hand-Foot Syndrome

The hand-foot syndrome is characterized by burning, painful swelling, and edema in the hands and feet. This syndrome may be the dose-limiting toxicity of 5-fluorouracil given by continuous intravenous infusion. Management requires dose interruption and/or downward dose-modification.

### Nonspecific Arthralgias

Patients who have completed various combination chemotherapy programs, often as adjuvant therapy for localized breast cancer, frequently have nonspecific arthralgias for months or years following the completion of chemotherapy. The syndrome is poorly characterized and described.

### Conclusions

Recognizing that a relationship exists between malignancy and rheumatic disease is important to our future understanding of the pathogenesis of the two entities. Oncogene activation is important in malignancy as well as in the normal differentiation of stimulated B cells, T cells, and peripheral blood mononuclear cells.\textsuperscript{54} Increased oncogene activation has been described in peripheral mononuclear cells of SLE patients compared with control subjects. Perhaps we can view autoimmunity disease as "benign proliferative diseases" related to accentuated growth of particular subsets of cells (ie, polyclonal B-cell proliferation in SLE, synovial proliferation including lymphoid elements, blood vessels and fibroblasts in RA, and massive proliferation of fibroblasts in PSS). Oncogenes also have structural homology and functions similar to growth factors (platelet-derived growth factor [PDGF] and epidermal growth factor). PDGF is the most important stimulator of fibroblast-like growth and is produced by the RA synovium.\textsuperscript{55} Transforming growth factor and PDGF are increased in sclerodermatous skin prior to the onset of fibrosis, thereby suggesting an early involvement of these growth factors.\textsuperscript{56}

Thus, oncogenes may activate cell division in malignancy or, similarly, "rheumogenes" may contribute to disregulation of both connective tissue and cell expansion in autoimmune disease. Rheumogenes could code either for abnormal or mutant growth factor or for an abnormal growth factor receptor devoid of self-modification. Further investigation into the relationship between malignancy and rheumatic disease may heighten our understanding of the pathogenesis, management, and possible prevention of these diseases.\textsuperscript{54}

### References