

# Extra-articular Manifestations in Rheumatoid Arthritis

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## ABSTRACT

Rheumatoid arthritis (RA) is a systemic autoimmune disease whose main characteristic is persistent joint inflammation that results in joint damage and loss of function.

Although RA is more common in females, extra-articular manifestations of the disease are more common in males. The extra-articular manifestations of RA can occur at any age after onset. It is characterised by destructive polyarthritis and extra-articular organ involvement, including the skin, eye, heart, lung, renal, nervous and gastrointestinal systems. The frequency of extra-articular manifestations in RA differs from one country to another. Extra-articular organ involvement in RA is more frequently seen in patients with severe, active disease and is associated with increased mortality. Incidence and frequency figures for extra-articular RA vary according to study design. Extra-articular involvement is more likely in those who have RF and/or are HLA-DR4 positive. Occasionally, there are also systemic manifestations such as vasculitis, visceral nodules, Sjögren's syndrome, or pulmonary fibrosis present. Nodules are the most common extra-articular feature, and are present in up to 30%; many of the other classic features occur in 1% or less in normal clinic settings. Sjögren's syndrome, anaemia of chronic disease and pulmonary manifestations are relatively common – in 6-10%, are frequently present in early disease and are all related to worse outcomes measures of rheumatoid disease in particular functional impairment and mortality. The occurrence of these systemic manifestations is a major predictor of mortality in patients with RA.

This paper focuses on extra-articular manifestations, defined as diseases and symptoms not directly related to the locomotor system.

**Keywords:** rheumatoid arthritis, extra-articular manifestations

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**R**heumatoid arthritis (RA) is the most common inflammatory joint disease, affecting 1-2% of the population worldwide, with women affected two to three times more commonly than men (1). Rheumatoid arthritis is a systemic inflammatory disease that can involve other tissues and organs as well as synovial joints. Rheumatoid arthritis is an inflammation of synovial tissue with symmetric involvement of peripheral joints, hand, feet, and wrists being most commonly affected. Rheumatoid arthritis can also affect non-articular muscular structures such as tendons, ligaments, and fascia (2).

Rheumatoid arthritis is associated with a high risk for morbidity and premature death secondary to the earlier development of cardiovascular, lung diseases and malignancy (3). Recent epidemiologic studies of extra-articular RA manifestations have emphasized their major role as predictors of premature mortality in patients with RA (4). Extra-articular manifestations are all the conditions and symptoms which are not directly related to the locomotor system (2,4,5).

Extra-articular RA is a serious condition, and rheumatoid arthritis patients with extra-articular manifestations should be aggressively treated and monitored (6). Extra-articular manifestations of RA occur in about 40% of patients, either in the beginning or during the course of their disease (7). There is no agreed classification for these manifestations and, because criteria and definitions vary so much, this paper includes not only the classic extra-articular features, but also the non-articular complications of RA, for example normochromic normocytic anaemia and chronic leg ulcers, and the important disease-associated comorbidities, including non-Hodgkin's lymphoma, ischaemic heart disease and osteoporosis (8). Systemic features in RA are frequent, mostly related to vasculitis, and often a reflection of longstanding inflammation. Most organs can be involved (9,10). These manifestations occur as frequent in men as in women, and may appear at any age. Many of these manifestations are related to the more active and severe RA, so early and more aggressive RA drug therapies are being employed and, although evidence from randomised studies is not available, this approach would seem appropriate in view of the adverse effect of extra-articular manifestations on RA outcomes (3,4,11,12).

Patients with RA, who have high titers of rheumatoid factor (ie, autoantibodies to the Fc component of immunoglobulin G) are most likely to have extra-articular manifestations of their disease, including rheumatoid nodules, rheumatoid vasculitis, and pleuropulmonary, neurologic, digestive, cardiovascular, cutaneous, hematologic, and ocular complications (13-15). Rheumatoid arthritis is one of the most prevalent connective tissue diseases and can be complicated by vasculitis with systemic manifestations (16,17). The prevalence of extra-articular manifestations of RA has declined in recent years, with the timing and pattern of the decline indicating that disease-modifying RA treatments may be changing the natural history of the disease (18-20).

Advances in the understanding of the pathogenesis of RA and development of new, more specific drugs may be of particular benefit to patients with extra-articular disease (21,22). Trends for specific extra-articular manifestations varied, showing liner declines in fibromyalgia syndrome, increases in RA lung disease (possible reflecting increased diagnostic sensitivity), and significant breakpoint declines in carditis and pooled serious extra-articular manifestations. Early recognition and treatment are important to decrease mortality (23,24).

This paper will briefly review extra-articular manifestations of RA with an emphasis on recent clinical research. □

## SKIN MANIFESTATIONS

**R**heumatoid nodules are the most frequent skin manifestations (20%) in RA. They occur mainly in rheumatoid factor positive RA patients and in early RA give risk to severe extra-articular manifestations. Histologically focal central fibrinoid necrosis with surrounding fibroblasts is observed: it is believed to occur as a result of small vessel vasculitis. Other manifestations of rheumatoid small vessel vasculitis affecting the skin are splinter haemorrhages, periungual infarcts, leg ulcers, digital gangrene and sharply demarcated painful ulcerations. They appear mostly at the lower extremities or where skin is exposed to pressure.

Skin manifestations are frequently associated with episcleritis, pleural and pericardial effusions. Early lesions show fibrinoid necrosis of the vessel wall, with an inflammatory cell infiltrate. Later on, artery wall fibrosis with occlu-

sion can appear. Subcutaneous nodules commonly occur on extensor surfaces subject to external pressure, for example, the upper forearm and elbow. Occasionally, they arise within the lungs or heart. Nodules are rare in seronegative RA (1-4,25-27). Pyoderma gangrenosum is a rare disease characterized by chronic, recurrent ulceration of non-infective origin and usually associated with rheumatoid arthritis. Pyoderma gangrenosum is a circumscribed necrotizing vasculitis of unknown etiology. Lesions associated with arthritis are often ulcerative. Although these lesions typically affect the lower limbs, they can also affect the entire body (28,29). □

### OCULAR MANIFESTATIONS

The most frequent is keratoconjunctivitis sicca, which affects at least 10% of patients. It is frequently observed together with xerostomia in a secondary Sjögren's syndrome (3). Episcleritis, inflammation of the layer superficial to the sclera, occurs in less than 1% of patients with RA and is generally a self-limiting condition. Scleritis is a more aggressive process, characterized by an intensely painful inflammation of the sclera itself. Peripheral ulcerative keratitis develops as an extension of scleral inflammation with involvement of the peripheral cornea and can lead to corneal melt (1,2,4,30,31). □

### ORAL MANIFESTATIONS

Oral dryness and salivary gland swelling can also be found in patients with RA. These patients can also develop secondary Sjögren's syndrome (3). □

### GASTROINTESTINAL SYSTEM

Gastrointestinal complications in RA are mostly iatrogenic and caused by medications. Primary involvement of the gastrointestinal tract, caused by mesenteric vasculitis leading to intestinal infarction, is very rare (3). This condition causes acute abdominal pain, and can lead to intestinal bleeding and perforation. There is no direct relation with arthritis activity, but as with other vasculitis, it is mostly observed in RA patients with high rheumatoid factor and subcutaneous nodules. Prognosis is poor and outcome frequently fatal (1,2,4). □

### PULMONARY MANIFESTATIONS

Pulmonary involvement in RA is frequent although not always clinically recognized. Pleural disease is common but usually asymptomatic; autopsy studies reported pleural involvement in 50% of cases, with only 10% clinically detected (5,32-35). Pleural effusions are usually exudates with mixed cell counts and high protein concentration. Multinucleated giant cells are highly specific but seen in fewer than 50% of the cases (6,36-38). The disease is frequently associated with exudative pericarditis, and with interstitial lung disease. Parenchymal pulmonary nodules generally are asymptomatic and found in RF-positive patients with nodules elsewhere (7,8,39). They can cavitate and cause pleural effusions. Pathological examination of the nodules reveals a central necrotic zone surrounded by a cellular area of proliferating fibroblasts (40). As with classical subcutaneous nodules, the underlying process appears to be a vasculitis. Interstitial lung disease is associated with RA; however, the prevalence and natural history are undefined. Diffuse interstitial pulmonary fibrosis in RA tends to occur more often in RF-positive male patients with longstanding nodular disease (9,10,41-43). □

### CARDIAC DISEASE

Rheumatoid arthritis patients are also more prone to heart conditions like the thickening of the artery walls (atherosclerosis) and heart attacks (44). Extra-articular manifestations of RA and the presence of traditional cardiovascular risk factors were also found. The risk for myocardial infarction in female RA patients is twice that of women without RA, and in long-standing disease of at least 10 years, the risk is 3 times higher. Pericarditis is the most common cardiac manifestation in RA (45-48). Although symptomatic pericarditis is relatively uncommon, autopsy studies revealed evidence of pericardial inflammation in 50% of the patients. It usually occurs in RF-positive patients with nodules and analysis of pericardial fluid reveals changes similar to those found in rheumatoid pleural effusions (49). Myocarditis (with presence of rheumatoid nodules) has been observed in autopsy studies, and myocardial fibrosis can lead to conduction abnormalities. Congestive heart failure may be more frequent than is clinically evident in RA (50). Endocardi-

tis with formation of rheumatoid nodules in the aortic or mitral valves can lead to valvular dysfunction. Arterial stiffness is an important factor in cardiovascular comorbidity in patients with RA. Rheumatoid arthritis is associated with decreased distensibility of the abdominal aorta in females, and such changes seem to correlate with disease severity (1-4,51-53). □

### RENAL DISEASE

Renal involvement in RA is rare, mesangial glomerulonephritis was the most common histopathological finding, whereas amyloidosis was the most common finding among patients with nephritic syndrome. Glomerulonephritis and interstitial renal disease are uncommon in the absence of vasculitis (3). Renal abnormalities are frequently iatrogenic (1,2,4). □

### NEUROLOGICAL MANIFESTATIONS

Peripheral neuropathy, presenting as diffuse sensorimotor neuropathy or mononeuritis multiplex, occurs in a small subset of patients with RA. The underlying mechanism is small vessel vasculitis of the vasa vasorum of the nerves with ischemic neuropathy and demyelination. These manifestations are part of the rheumatoid vasculitis syndrome. Cervical myelopathy, caused by atlantoaxial subluxation or pannus formation, occurs frequently in RA patients with severe and longstanding disease (7,54,55). □

### HAEMATOLOGIC MANIFESTATIONS

Patients with RA may present with haematological abnormalities either at the time of diagnosis, or during the course of their illness. Haematological manifestations in RA can be broadly categorized into areas of anaemia, neutropenia, thrombocytopenia, thrombocytosis, eosinophilia, and haematological malignancies (56). Anaemia is, by far, one of the most common extra-articular symptoms of RA. The cause of anaemia in RA is multifactorial-disease

activity, drug-induced, nutritional, gastrointestinal bleed, bone marrow suppression, and ineffective erythropoiesis (57). Anaemia of chronic disease is observed in RA, where it usually correlates with the disease activity, particular the degree of articular inflammation. It is normochromic and normocytic. Eosinophilia in RA reflects active disease or hypersensitivity to drugs (58). Thrombocytosis is a frequent finding in active RA and is correlated with the number of active inflamed joints (59). Lymphadenopathy is sometimes observed in active RA, usually presenting on biopsy as benign follicular hyperplasia (12-14,60). □

### CONCLUSIONS

Rheumatoid arthritis is a chronic systemic disease of unknown etiology characterized by articular involvement, extra-articular involvement, and the presence of serum rheumatoid factor. In RA, there is a symmetric and persistent inflammation of the synovial tissue, usually involving the peripheral joints. Although considered a "joint disease" rheumatoid arthritis is associated with involvement of extra-articular manifestations. Prevalence of these manifestations is about 40% of patients at any time during the course of the disease; almost all manifestations are a consequence of longstanding active disease (vasculitis). Extra-articular RA is a serious condition, and RA patients with extra-articular manifestations should be aggressively treated and monitored. Currently, there are no reliable predictors for these features in early RA, although they are associated with men, smokers, more severe joint disease, and worse function. The longer the duration of the disease will be, the larger the number of extra-articular manifestations. Extra-articular manifestations in RA were present in a substantial proportion of patients, which lead to a worse disease outcome. Anaemia, thrombocytosis and respiratory system involvement were the commonest. They need to be recognised early and managed promptly. □

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