An Overview of the Extraarticular Involvement in Rheumatoid Arthritis and its Management

Subham Das, Prasanta Padhan
Department of Pharmacology, Gouridevi Institute of Medical Sciences and Hospital, Durgapur, West Bengal, Department of Rheumatology, Kalinga Institute of Medical Sciences, Bhubaneswar, Odisha, India

Abstract

Rheumatoid arthritis (RA) is an autoimmune systemic disease characterized by long-standing inflammation and significant joint destruction. Despite significant research and success toward the treatment modalities, complete remission still remains a challenge. Even then a number of early and late extraarticular manifestations (EAMs) of the disease further complicate the disease progression. Various EAM encountered in RA can involve more than one organ or system in the body and their clinical features also show lot of variations, mostly involving cutaneous, cardiovascular, and pulmonary systems. The mortality associated with EAM may also be quite high in RA, sometimes more than the disease itself. These EAMs are difficult to diagnose and even more difficult to treat since no clear consensus exists among the rheumatologists as to their correct classification and also due to the fact that no clearcut guidelines are available for their treatment. With this background knowledge, the present review focuses on the various EAMs of RA, their classification, clinical features, and general management overview.

Keywords: Classification, extraarticular manifestation, EAM, remission, rheumatoid arthritis

INTRODUCTION

Rheumatoid arthritis (RA) is a common systemic inflammatory disease characterized by the presence of destructive polyarthritis with a predisposition for affecting the small joints of the hands and feet (though the disease process can virtually affect any synovial joint). The prevalence of RA ranges from 0.5% to 2% among the general population, mostly affecting women who are two times more susceptible than men in the fourth to fifth decades of life. There is neither exact definition of RA nor a pathognomonic test. The diagnosis of RA, therefore, rests on a composite of clinical and laboratory observations. RA is extremely heterogeneous with respect to severity and progression. Permanent remission can occur but is rare once there is a significant amount of joint damage. Although RA is predominantly an articular disease, it is important to remember that there are a number of extraarticular manifestations (EAMs) associated to the disease, for example, involvement of the eyes, lungs, skin, and nervous system. In fact, nearly 50% of patients with RA develop some kind of EAMs of RA. Although RA itself results in significantly reduced survival among those affected, mortality rates are further increased in those having EAMs. Proper diagnosis and appropriate management of EAM, therefore, play a crucial role in this scenario. This short review will give an overview of the various EAMs of RA and their appropriate management so as to minimize the added mortality due to the EAMs.

CLASSIFICATION OF THE EXTRAARTICULAR MANIFESTATIONS IN RHEUMATOID ARTHRITIS

EAM can affect various body organs; however, they can be quite distinct from the common ailments in that particular body organ or tissue. Although there is existence of the Malmö criteria that distinguishes the EAM into severe and not severe categories, there is a lot of debate and lack of clear consensus among rheumatologists as to the correct classification and also due to the fact that no clearcut guidelines are available for their treatment. With this background knowledge, the present review focuses on the various EAMs of RA, their classification, clinical features, and general management overview.

Address for correspondence: Subham Das, Department of Pharmacology, Gouridevi Institute of Medical Sciences and Hospital, Durgapur - 713 212, West Bengal, India.
E-mail: drsubhamdas2009@gmail.com

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exact applicability of that criteria.\textsuperscript{[5]} Although the common characteristic is that severe EAMs are usually associated with significantly more morbidity and mortality; however, that is not always true.\textsuperscript{[6]}

For the benefit of discussion and also to classify the EAMs in a simpler way, it might be a better option to classify them according to their prevalence in RA patients [Table 2].

EAMs in RA remain a serious problem to the treating clinicians owing to their complex presentation and diagnostic difficulties, raising therefore, a need to treat them aggressively and also a need for intense and frequent monitoring of individual cases. EAM can present as a diagnostic dilemma as drug-induced toxicities and associated infections frequently mimic having similar presentations. EAMs occur in about 50% of RA patients, while the life expectancy is reduced by approximately 7 years in males and 3 years in females.\textsuperscript{[7]} The incidence of EAM in RA varies widely among various studies mostly because of diverse nature of studies done. In some cases, there were lack of consensus about case definition as to the inclusion of all EAM or only severe ones, few inconsistencies are also due to variations between community-based and hospital-based studies as the hospital-based studies tend to include more severe and complex presentations and probably due to aggressive management.\textsuperscript{[8,9]} EAM can occur at any time during the disease while few common EAM are even notorious for appearing early. Most cases of premature death in EAM have been associated with cardiovascular complications, lung diseases, and malignancy.\textsuperscript{[10]} Unlike RA, there is no particular sex predilection in case of EAM, occurring equally in males and females and appearing at any age. Generally, those RA patients having high titers of rheumatoid factor,\textsuperscript{[11]} antinuclear antibodies,\textsuperscript{[12]} disease-associated human leukocyte histocompatibility antigen (HLA) genes (especially homozygous DRB1*04 subtype),\textsuperscript{[13]} history of smoking,\textsuperscript{[14]} etc., are most likely to have EAM which includes rheumatoid nodules, vasculitis, pulmonary, neurologic, cardiac, hematological, and cutaneous complications.\textsuperscript{[2,15]} The presence of anti-CCP antibodies is also associated with a more progressive joint damage and severe EAM.\textsuperscript{[16]} A genetic association that has been linked to EAM is homozygosity for HLA class II DRB1*04,\textsuperscript{[17]} tyrosine-phosphatase gene PTPN22,\textsuperscript{[18]} and epigenetic changes.\textsuperscript{[19]} Although from various observational studies, it is suggested that RA is becoming a less severe disease now-a-days, probably because of the advent and early usage of newer and more efficacious disease-modifying antirheumatic drugs (DMARDs) or biologics,\textsuperscript{[20]} unfortunately, the same cannot be said about the EAM which remains a serious challenge to the rheumatologists as well as to the patients.

### Table 1: Extraarticular manifestations in rheumatoid arthritis, according to Malmö criteria\textsuperscript{[8]}

| Affected tissue or organ | Nonsevere EAM | Severe EAM |
|--------------------------|---------------|------------|
| Skin                     | Nodules       | Petechiae, purpura, ulcers, gangrene |
| Pulmonary system         | Bronchiolitis obliterans | Pleuritis |
| Heart                    | Valvular heart disease | Interstitial lung disease |
| Heart                    | Myocarditis    | Pericarditis |
| Heart                    | Arrhythmias    | Coronary vasculitis and aortitis |
| Nervous system           | None identified | Mono/polyneuritis multiplex |
| Eyes                     | Secondary Sjögren’s syndrome | Central nervous system vasculitis |
| Hematological system     | None identified | Episcleritis or scleritis |
| Renal system             | None identified | Retinal vasculitides |
| Musculoskeletal system   | None identified | Felty’s syndrome |

EAM=Extraarticular manifestations, RA=Rheumatoid arthritis

### Table 2: Classification of extraarticular manifestations in rheumatoid arthritis as per frequency

| Commonly encountered EAM | Uncommon EAM |
|--------------------------|--------------|
| RA nodules               | Lung fibrosis |
| Lymph node enlargement*  | Felty syndrome |
| Splenomegaly*            | Myositis |
| Pleuritis*               | Vasculitis |
| Pericarditis*            | Scleritis |
| Osteoporosis             | Cord compression |
| Carpal tunnel syndrome*  | Lymphoma |
| Sicca syndrome*          | Secondary amyloidosis |

*Occur early in disease course. EAM=Extraarticular manifestations, RA=Rheumatoid arthritis

### Organ Involvements in Rheumatoid Arthritis

The various organ and systems involved in RA and the EAM seen thereof are listed in Table 3. However, details of such involvements including their pathophysiological features and prevalence are given below in a concise manner.

#### Cutaneous involvement

Rheumatoid nodules are the principal cutaneous manifestation occurring in up to 30% of RA patients with EAM. They are mainly found on the extensor surface of the forearm and also over pressure areas throughout the skin. Nodules, though not specific for RA, but are useful adjuncts in diagnosis and prognosis, which correlate with seropositivity, disease activity, and disease progression. It is mainly believed to occur due to small vessel vasculitis, other such manifestations being splinter hemorrhages, periungual infarcts, digital gangrene, and painful ulcers also,\textsuperscript{[21]} presenting as Raynaud’s phenomenon. Important point to note in this regard is that if Raynaud’s phenomena appear long after the onset of RA, it generally leads to a more severe disease course.\textsuperscript{[22]} Apart
from those, palmar erythema is also fairly common in RA. Leukocytoclastic vasculitis also occurs and is seen as palpable purpura which mostly shows spontaneous improvement with RA treatment.

**Lymph node enlargement**

Lymph nodes are often enlarged in RA but are rarely palpable. Epitrochlear lymph nodes are commonly enlarged in those who have significant arthritis involving joints of hands. In a few cases, RA may present with widespread nodes mimicking Hodgkin’s disease.

**Pleuropulmonary involvement**

Pleuritis is a common EAM in RA, often in milder form but difficult to identify clinically, affecting almost 5%–10% of RA patients. A diverse variety of clinical pictures may represent the pulmonary system involvement in RA that encompass pleural effusion, interstitial lung disease (ILD), rheumatoid pulmonary nodules, small airway disease, etc. Exudative pericarditis and ILD very often are found along with RA. But like other pulmonary and cardiac manifestations, they are more common in the older patients. Clinically significant ILD is prevalent in about 7.7%–12% of RA cases. The primary patterns of ILD in RA patients happen to be usual interstitial pneumonia (UIP) and nonspecific interstitial pneumonia (NSIP) that are observed both histologically as well as radiologically. With regard to the prognostic point of view, the presence of UIP in RA has been associated with a poor prognosis than NSIP, more RA disease severity, and a reduced survival. The management options in most cases of rheumatoid ILD consist of biological DMARDs with a careful monitoring with high-resolution computerized tomography (HRCT) scans. A combined approach of a rheumatologist, pulmonologist, and radiologist ensures a better and effective care to such cases. Pleural effusion if occur is mostly bilateral. Rheumatoid pulmonary nodules are another important finding which are asymptomatic and found almost exclusively in seropositive RA patients. Radiographically, they are coin-shaped lesions that can be difficult to differentiate from malignancy. To confirm the diagnosis, therefore, in patients in whom malignancy is clinically suspected, further imaging or tissue biopsy may be warranted. Diffuse interstitial fibrosis and fibrosing alveolitis are rarely associated with RA. In few extremely rare cases, methotrexate use is also associated with the development of pulmonary fibrosis. HRCT is by far the best approach for early diagnosis of pulmonary EAM in RA. The mainstay of treatment in pulmonary EAM is based on systemic steroids and immunosuppressive therapy in the form of mycophenolate or cyclophosphamide and azathioprine although in very severe presentations or in case of an unresponsive disease, rituximab therapy is also common.

**Cardiovascular system**

There is increasing evidence that patients with RA suffer from the increased cardiovascular disease independent of the traditional risk factors. The more prevalent manifestations include atherosclerosis, myocardial infarction, pericarditis, arrhythmias, and valvular heart disease. The most common EAM in cardiovascular system is pericarditis, usually associated with seropositive RA patients. In fact, symptomatic pericarditis can even be the first sign of RA. Most of the cardiac manifestations are silent and rarely need treatment. In symptomatic pericardial disease, steroids or nonsteroidal anti-inflammatory drugs (NSAIDs) may bring about rapid improvement. Inflammation is thought to play a key role in the development of atherosclerosis and the systemic inflammatory response in RA may explain the link. An earlier work by the same authors has established possible beneficial role of adjunct statins in the management of RA; statins by their pleotropic actions on a variety of inflammatory and immune mediators may be particularly helpful not only in the RA disease amelioration but also reducing the cardiologic and vascular EAM in RA. Epidemiological studies reveal that cardiovascular mortality is increased in patients with early and established disease, and is surprisingly, worse in women, a group traditionally put at lower risk of having cardiovascular mortality. Another important manifestation that is clinically less evident but frequently associated with RA is congestive heart failure. Formation of rheumatoid nodules in mitral or aortic valve can sometimes lead to valvular heart disease.

**Ocular manifestations**

The most common ocular manifestation in RA is the presence of sicca syndrome or keratoconjunctivitis sicca, affecting at least 10% of patients, frequently associated with dry mouth, salivary gland swelling, and secondary Sjögren’s syndrome. Treatment of which is often symptomatic with artificial tear and/or saliva supplements based on evaluation. Rheumatoid vasculitis also gives rise to a severe form of painful scleritis, leading to scleromalacia. Prompt treatment with high-dose steroids can salvage vision in such cases. On the other hand, episcleritis, which is an inflammation in the superficial layer
to sclera, is benign and usually resolves spontaneously. Recent studies reveal reduction in ocular manifestations with the use of rituximab and other biologic agents, but clinical trial data are not yet available.\(^{[38]}\)

**Neurological involvement**

The most common neurological involvement in RA is entrapment neuropathy developing secondary to synovitis. Median nerve compression can occur early in the disease. In fact in every patient with carpal tunnel syndrome,\(^{[39]}\) the diagnosis of RA should be kept in mind. Other nerves getting entrapped in RA are rare and include posterior tibial nerve at tarsal tunnel and ulnar nerve at elbow. Mononeuritis multiplex, a peripheral but often bilateral neuropathy, can also present acutely in RA.\(^{[40]}\) This is a manifestation of systemic rheumatoid vasculitis that warrants urgent evaluation and intervention. Clinically, this presents with wrist drop and foot drop. A sudden onset of peripheral sensorimotor neuropathy can signal the presence of aggressive rheumatoid vasculitis and thereby poorer prognosis. Treatment includes high doses of intravenous (IV) steroids with IV cyclophosphamide. Cervical subluxation at the atlantoaxial level\(^{[41]}\) can be present in about one-third of the long-standing RA patients but is usually asymptomatic. Another rare but serious EAM is cervical myelopathy due to cervical instability which can be fatal. Symptoms include paresthesia, weakness, paralysis, sensory loss, incontinence, and syncope.

**Osteoporosis and fractures**

Various cytokines which are generated as a result of inflammatory process in RA, encourage bone resorption by inducing osteoclast action, and lead to osteoporotic changes.\(^{[42]}\) However, other additional risk factors such as physical inactivity, difficulty in walking with deformed lower limb joints with increased incidence of falls, Vitamin D deficiency, and preexisting osteoporosis contribute to spontaneous fractures. Use of systemic as well as intraarticular corticosteroids further increases fracture risk due to osteoporosis.

**Tendons and ligaments**

Spontaneous rupture of tendons and ligaments, most commonly at the wrist, hand, and rotator cuff are occasionally encountered in RA. More often, tenosynovitis and weakening of ligaments lead to joint instability and subluxation.

**Renal involvement**

Renal involvement is relatively rare in RA. This EAM might be a consequence of antirheumatic drugs itself, especially of NSAIDs and DMARDs.\(^{[43]}\) Apart from that, long duration of disease and poor response to therapy are important risk factors for this EAM. Mesangial glomerulonephritis is the hallmark of renal involvement in RA in about 60% of cases.\(^{[44]}\) In patients in whom renal involvement is present, secondary amyloidosis appears to be the most common feature. However, intensive antirheumatic therapy now gives a more favorable outcome, rituximab being a good choice for this condition.

**Felty’s syndrome**

This is the most common type of hematological EAM in RA that may be present at the time of diagnosis or can occur during treatment. There is association of splenomegaly and neutropenia in typically those patients who have rather destructive RA.\(^{[45]}\) Systemic disease, hepatomegaly, and lymphadenopathy are also common. Most of the patients having this EAM generally have rheumatoid factor positivity.\(^{[46]}\) In uncomplicated cases, treatment is mainly conservative with methotrexate, splenectomy remaining a controversial option and often offer only transient benefit in these patients.\(^{[47]}\)

**Large granular lymphocyte syndrome**

Although similar in presentation with Felty’s syndrome, it is differentiated by the presence of large granular lymphocytes and a clonal lymphocytosis.\(^{[48,49]}\) The arthritis that accompanies LGL syndrome is typically less destructive than that seen with Felty’s although this is not always the case.

**Drug toxicities**

Although not a true EAM of RA, drug toxicities of medications used in RA need special consideration. Various adverse drug reactions are also common as the drugs have to be used continuously and for prolonged period. Clinical and laboratory monitoring for the side effects of DMARDs,\(^{[50,51]}\) and also for NSAIDs are extremely important. Complete blood counts and liver and renal function tests are mandatory as per the guidelines, initially every month for the first 3 months and every 3 monthly thereafter.\(^{[52]}\)

**Conclusion**

In spite of the common notion that severe EAM in RA may be on the declining trend because of the current biologic therapy, there is a significant lack of published reference and guidelines in its support. Major therapeutic guidelines are mostly based on nonrandomized trials as the patients with EAM were mostly excluded from controlled clinical trials where newer biologics were compared head to head against conventional DMARDs. Even there is no clear consensus till now as to a universal classification of EAM in RA. Keeping in mind, the diverse EAMs that are encountered in RA, a clear consensus regarding its definition, classification, and management should be the need of the hour.

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There are no conflicts of interest.

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