IJNRD.ORG ISSN : 2456-4184
INTERNATIONAL JOURNAL OF NOVEL RESEARCH AND DEVELOPMENT (IJNRD) | IJNRD.ORG
An International Open Access, Peer-reviewed, Refereed Journal

EXTRA ARTICULAR MANIFESTATIONS AND ITS MANAGEMENT IN RHEUMATOID ARTHRITIS: AN OVERVIEW

[1]*Purvi Mehta, [1]Gulam Mohiyuddin N Shirol, [1]Neeraj Hiremath
[1]Pharm D Interns
[1]Department of Pharmacy Practice, KLE College of Pharmacy, Vidyanagar, Hubballi – 580031
***Corresponding Author: Purvi Mehta**, Pharm D Intern,
Department of Pharmacy Practice, KLE College of Pharmacy, Vidyanagar, Hubballi

Abstract: Rheumatoid Arthritis [RA], an immune-mediated illness, results in ongoing, low-grade inflammation that can eventually destroy joints and result in deformity, disability, and even death. Although periarticular and osteoarticular symptoms are the primary RA symptoms, RA is a systemic disorder that appears with cutaneous and organ-specific extra-articular manifestations [EAM]. Extra-articular symptoms are known to cause a number of potentially detrimental long-term consequences. High disease activity in RA has been associated with an increased risk of these characteristics. However, because these extra-articular symptoms are frequently associated with more severe and active RA and because these patients have a poor prognosis, an aggressive treatment strategy is usually adopted. Since the effectiveness of medication therapy for EAM has not been well investigated in randomized clinical research, practitioners still find it difficult to comprehend the complexity of EAM and how to manage them. The fact that there is no clear understanding among rheumatologists about how to categorize these EAMs or that there are no standardized methods for treating them makes it difficult to evaluate and much harder to treat these EAMs. In our initial categorization effort, we divided EAM into cutaneous and visceral subtypes, both severe and not severe, and classified them accordingly. In light of this background, the current study focuses on the various EAMs of RA, their classification, clinical characteristics, and general management overview.

Keywords: Rheumatoid arthritis, Extra-articular manifestations, Autoimmune disorder

Introduction

Rheumatoid arthritis is a chronic, systemic, inflammatory, and autoimmune disease that causes symmetrical polyarthritis, characterized by joint degradation, erosions, inflammation, and bone loss of both large and small joints and commonly manifested between the ages of 30 and 50 [1]. In the general population, its prevalence ranges from 0.5% to 2% [2]; particularly affecting women who are two times more susceptible than men in the fourth to fifth decades of life [3], smokers and people with a family history of the condition [4]. Although the etiology of rheumatoid arthritis is complicated and involves both environmental and genetic factors, it is not fully elucidated. The severity of a disease is also influenced by genetics [5]. Joint inflammation is caused by a triggering factor, that could be autoimmune or infectious. Joint degeneration and systemic consequences are mediated by extensive interactions among several immune cell types and their cytokines, proteinases, and growth factors [5]. There is neither a characteristic clinical test nor a clear definition of RA, therefore, a combination of clinical and laboratory findings underpins the diagnosis of RA [6]. Rheumatoid arthritis is generally diagnosed by clinical means. The usual presentation is polyarticular, with several joints complaining of pain, stiffness, and swelling in a bilateral, symmetric pattern.[7] The diagnosis of rheumatoid arthritis cannot be obtained by a single test. Complete blood count with differential, rheumatoid factor, and erythrocyte sedimentation rate or C-reactive protein should all be performed as part of initial laboratory testing. [8]

Although RA is primarily an articular disease, it's essential to note that the condition can also have a number of "extraarticular manifestations" [EAMs] [6], that includes the heart, kidney, lung, digestive system, eye, skin and nervous system. Arthritis is the most noticeable symptom in the majority of people with adult-onset rheumatoid arthritis [RA], many patients may experience extraarticular signs [9]. Extraarticular manifestations occur more frequently in people who have higher rheumatoid factor levels and are connected with patients who have positive rheumatoid factor because large volumes are frequently accompanied by rheumatoid nodules and in these patients, extraarticular manifestations are typical [9]. The prevalence of extra-articular manifestations is estimated to be from 17.8 to 40.9% of all RA patients[10]. Due to the early onset of heart, vascular, lung ailments and malignancies, rheumatoid arthritis is linked to a significant risk of morbidity and premature mortality [11]. Recent epidemiologic studies have highlighted the importance of extra-articular RA symptoms as indicators of early death in RA patients [12]. All diseases and symptoms that have no connection to the locomotor system directly are referred to as extra-articular manifestations. [12,13,14]

Regardless of the fact that RA itself substantially reduces overall survival among people afflicted, EAMs further raise death rates [15]. Therefore, a proper diagnosis and management of EAM are very crucial in this situation.

This paper will briefly review on overview of the various EAMs of RA and related therapy.

Classification Of Extraarticular Manifestations in Rheumatoid Arthritis

A range of organ systems may be affected by EAM; however, they may not have the same symptoms as those that are typically present in that organ or tissue. The Malmö criterion, which classifies the EAM into groups of severe and not severe [Table 1], may exist, but rheumatologists' debate about how precisely these criteria should be used, and there is a lot of conflict in this area [10]

Severe EAM are often related to significant co-morbidity and premature mortality [16]. Although evidence from a number of observational studies suggests that RA is becoming a less severe disease today—likely as a result of the development and early application of newer and more effective disease-modifying antirheumatic drugs [DMARDs] or biologics [17] —the same is not true for EAM, which continues to pose a significant challenge to both rheumatologists and patients.

Cutaneous manifestations

Skin manifestations are the most prevalent presentation in patients with severe RA. There are a range of classifications for skin lesions based on clinical, histopathological, or a combination of these factors. [18-20]

The lesions of cutaneous manifestations can be broadly classified as following:

- Specific to RA: RA nodules, RA vasculitis
- Non-specific to RA: Purpura, leg ulcers, urticaria etc.
- Common dermatological disorders overlapping with RA
- Drug-induced adverse effects[21]

Rheumatoid nodules are the most common cutaneous manifestation seen in up to 30% of RA patients with EAM [22] and are 90% more frequent in RF-positive individuals than RF-negative individuals [incidence] [27]. Smoking, RF positive, and HLA-DRB1 homozygosity are independent risk factors for nodular manifestations [33]. Rheumatoid nodule frequency is found to be correlated directly with RF titer and less with the actual intensity of the clinical presentation, making RF a predictor of the development of nodules[27]. They are mostly seen on pressure points across the skin and on the forearm's extensor surface [6]. It is mostly thought to be caused by small vessel vasculitis, although it can also appear as painful ulcers, splinter hemorrhages, digital gangrene, periungual infarcts, and periungual infarcts [24], presenting as Raynaud's phenomenon. Rheumatoid nodules frequently indicate more severe extra-articular systemic symptoms, which has a negative clinical impact [25]. Patients have a lower chance of going into remission and are more prone to develop vasculitis [26]. Nodules are often asymptomatic, thus special treatment is not needed. If nodules are incapacitating, ulcerated, infected, obstructing a nerve, or producing a restricted range of joint motion, surgical excision may be an option.[27] The size of the nodule can be reduced by therapy with oral corticosteroids or by injecting corticosteroids directly into the nodule. Older and bigger nodules, nevertheless, might not be affected. [28]

In Rheumatoid vasculitis, Blood vessels are affected by inflammation, leading to a variety of clinically relevant skin and systemic issue [27]. It frequently occurs in a chronic condition [10 to 14 years after the

beginning of arthritic symptoms] and is correlated to rheumatoid nodules [29]. Up to 43% of rheumatoid vasculitis patients may have significant morbidity and death, particularly in the first six months following the development of the condition. Increased RF levels are linked to higher mortality [29-31]. To treat rheumatoid vasculitis, glucocorticoids and cyclophosphamide have often been used [30,31]. Rituximab and anti-TNF medications have also been studied as potential treatment alternatives. [32]

Cardiac manifestations

The main cause of morbidity and death in RA patients is cardio-vascular disease, which is an independent significant predictor for RA [34]. Patients with RA have a 50% higher prevalence of cardiovascular-related mortality and a roughly 50% increased risk of cardiovascular events compared to the general population [34,35]. Atherosclerosis, myocardial infarction, pericarditis, arrhythmias, and valvular heart disease are some of the usual cardiac manifestations. It is well understood that the inflammatory component of rheumatoid arthritis and cardiovascular risk factors may interplay to enhance the cardiovascular burden of RA patients [36-38].

The most prevalent EAM in the cardiovascular system is pericarditis, which is typically associated to RA patients who are seropositive [39]. In fact, pericarditis with symptoms may be RA's initial warning flag [40]. Rheumatoid pericarditis still has uncertain underlying pathogenic etiology [9]. Sharp pleuritic chest discomfort, pericardial friction rubs, and, in extreme cases, pericardial tamponade are all symptoms of the condition [41]. Most cardiac complications associated with RA are asymptomatic and do not necessitate treatment. Non-steroidal anti-inflammatory medications or steroids may speed up the resolution of pericardial illness that is symptomatic, with dull chest discomfort or pericardial effusion without hemodynamic compromise [42]. Additionally, colchicine is recommended by ESC guidelines as first-line therapy in addition to NSAIDs since dual therapy may reduce symptoms and the probability of recurrence [43]. Secondly, GCs may be considered as an additional therapeutic choice for pericarditis treatment in RA patients [43,44]. Other commonly observed cardiac manifestations include pericardial effusion and cardiovascular autonomic dysfunction [CAD], in which RA patients are at higher risk of having pericardial effusion characterized by accumulation of pericardial fluid. The treatment option remains same as Rheumatoid pericarditis [44]. RA patients may also have signs of CAD, typically recognized by an extended QT interval on the ECG [45]. Because ventricular arrhythmias are linked to QT prolongation, it is a valuable predictor of elevated risk for cardiovascular death [45]. Regarding potential treatments, Tocilizumab [TCZ], given once every four weeks to 13 RA patients with QT prolongation, shortened the QTc interval to mean values of 440 msec while also lowering CRP levels [46]. These results focus on potential value of immunomodulatory treatments in treating these cardiac conduction abnormalities in RA despite the limited sample size and brief follow-up period [46]. Endocarditis, myocarditis, and amyloidosis are relatively rare complications of RA.

Pulmonary / Pleuropulmonary manifestations

Pulmonary manifestations are one of the main causes of morbidity and premature mortality during the RA disease [47,48]. In fact, after cardiovascular complications and comorbidities, the pulmonary disease has been recognized as an important cause of death on these patients [49] and the prevalence of the pulmonary disease ranges between 5% and 30% [50]. Patients with rheumatoid arthritis [RA] may experience a wide range of pulmonary manifestations that can affect any intrathoracic compartment, including the lung parenchyma, pleura, airways, and the pulmonary vasculature [51]. In terms of clinical manifestations, lung involvement can take the form of various patterns of interstitial lung disease [ILD], pleural disease, rheumatoid nodules, upper airway illness [such cricoarytenoiditis], or lower airway disease [such as follicular bronchiolitis] [52]. Interstitial Lung Disease [ILD] is a prevalent characteristic of RA, and the estimated prevalence of the condition rises with disease duration [53,54]. Although genetic, humoral, and environmental variables appear to be involved, the exact cause of RA-ILD is unknown [55-57]. The potential ILD-promoting actions of several RA medications, such as cs- and b-DMARDs, as well as many environmental factors [smoking habits, irritants] complicate the pathogenic scenario of RA-ILD [58]. It may be present and asymptomatic and progresses slowly [59]. The most frequent signs and symptoms are a dry, ineffective cough and shortness of breath, especially after exercise [60]. In fact, in the early stages of RA, pulmonary EAM rarely present any symptoms. High resolution computed tomography [HRCT] is the best method for a quick diagnosis of lung involvement [61]. As of now, there are no defined consensus treatment guidelines to direct clinicians in the clinical medical treatment of RA-ILD [62]. Usually, systemic steroids and immunosuppressive therapy in the form of mycophenolate, cyclophosphamide, and azathioprine are the mainstay of treatment for pulmonary EAM, though rituximab therapy is also frequently used in cases of extremely severe presentations or when the disease is not responding to other treatments [6].

The most prevalent manifestations of RA pleural illness are pleural effusion, pleuritis, and pleural nodules; pneumothorax is a rare symptom [63,64]. Pleuritis is a typical EAM in RA, sometimes in a milder form that is difficult to detect clinically, affecting approximately 5%-10% of RA patients [65]. RA patients usually complain fever and chest pain if symptomatic. The initial examination of RA pleural effusion comprises a chest radiograph that shows costophrenic angle blunting [66]. The properties of the fluid can be assessed using ultrasound. A "rheumatoid effusion" is typically an exudate with low pH, low glucose, and increased lactate dehydrogenase levels [63,67]. Usually, these pleural effusions cure on their own within a few weeks or with treatment for RA. If small and asymptomatic, no treatment is required; however, persistent pleural inflammation can lead to pleural thickening, trapped lung, and potential infections. Thoracentesis, intrapleural GC instillation, or systemic GC administration may be regarded as treatment options for individuals with substantial and symptomatic effusions [68].

Ocular manifestations

Episcleritis, scleritis, keratitis, dry keratoconjunctivitis and retinopathy are a few common ophthalmic rheumatologic manifestations [69]. This manifestation affects between 25–39% of individuals and, in some cases, it serves as the disease's initial warning sign [70]. In individuals with a long-term illness, the likelihood of ocular involvement rises as the disease progresses, and it may be the primary clinical symptom [70,71]. Ocular involvement in RA may indicate a more severe form of the condition as the eye is a favored immune site and that immunosuppressive [this state may sustain tolerance to external stimuli] components make up its microenvironment [72].

Episcleritis is a condition in which the episclera, a thin layer of tissue that covers the sclera, becomes inflamed and irritated. It is a very common disorder with little or no risk of blindness and mild pain. RA is one of the main possible causes among many other possible factors, infectious disorders like syphilis and tuberculosis should also be considered [73]. Clinically, an edema of the episclera is visible, either diffuses or localized, especially around the episcleral blood vessels [74]. No specific therapy is required because the illness is typically benign; however, topical GCs such fluorometholone or loteprednol etabonate are used to treat symptomatic episcleritis. In order to resolve the clinical picture, this therapy may be given four times per day for one to two weeks [75]. NSAIDs, such as ibuprofen or naproxen, may be provided in the event of a lack of response [76,77]. Episcleritis often recurrent and can occasionally migrate to the sclera, which causes scleritis [78].

Scleritis is an inflammation of the sclera that might lead to vision loss. Clinically, it appears as a persistent eye irritation that radiates to the face and scalp, which often gets worse at night and is accompanied by blurred vision and red eyes. Usually, the anterior portion of the sclera is more frequently affected [79]. Diffuse, nodular, necrotizing anterior scleritis can occur with or without inflammation [73]. All patients need systemic therapy, often in the form of non-steroidal anti-inflammatory medications [NSAIDs] or corticosteroids, but if a systemic autoimmune illness is present, cyclosporine A should be administered topically or orally to begin a particular course of treatment [80]. NSAIDs can be used to treat anterior scleritis [81], but systemic GCs, with a suggested starting dosage of 1 mg/kg per day, are needed to treat necrotizing condition [81]. A randomised controlled study looking at rituximab in refractory scleritis demonstrated benefit and safety. Biologic drugs have shown to be useful in treating severe instances of recurrent and refractory scleritis [82].

As a result of scleral inflammation spreading to the peripheral cornea, peripheral ulcerative keratitis occurs and has the potential to cause corneal melt [83]. The sicca syndrome of Sjogren, also known as keratoconjunctivitis sicca also called as dry eye syndrome, is linked to the most prevalent ophthalmological symptoms of RA [3]. As a result of this ocular involvement in RA, the lachrymal film may become unstable and alter in quality [84]. The initial course of treatment for dry eye syndrome involves artificial tears. To promote salivary or lachrymal production, systemic treatments like pilocarpine may also be employed [84]. If individual does not include Sjogren syndrome, the most common eye involvement is scleritis and/or episcleritis [3].

Hematological Manifestations

The major categories of haematological symptoms in RA include anaemia, neutropenia, thrombocytopenia, thrombocytosis, eosinophilia, and haematological malignancies [85]. Felty’s syndrome is the most prevalent form of haematological EAM in RA, which might be present at the time of diagnosis or develop during therapy [6]. Felty's syndrome, can worsen up to 3% of RA patients, is traditionally characterised by the triad of RA, neutropenia, and splenomegaly. Only chronic idiopathic neutropenia with an absolute neutrophil count of less than 1,500/mm3 may be used to diagnose and is the hallmark of Felty's syndrome, suggesting splenomegaly and significant joint involvement may not always be present [86]. Patients who have destructive arthritis,

seropositive RA, and a prolonged history of the disease are often affected [87]. Such individuals are more likely to develop rheumatoid nodules, infections, and systemic extra-articular disease symptoms such vasculitis and peripheral neuropathy [9]. Clinically, compared to RA patients without Felty's syndrome, those with the condition have a higher frequency of extra-articular rheumatoid nodules, lymphadenopathy, hepatomegaly, anaemia, and thrombocytopenia [88]. Sulfasalazine, hydroxychloroquine, and MTX are the mainstays of the treatment for Felty's syndrome; in non-responder patients, rituximab may also be an alternative [89]. Additionally, neutropenia and recurring infections should be taken into account. Recombinant granulopoietic growth factors may then be provided [89]. Due to a higher prevalence of post-splenectomy infections, splenectomy is rarely thought of as an early treatment choice [90].

Renal manifestations

Renal involvement is a rare EAM of RA [91]. The two primary causes of renal impairment in RA are secondary amyloidosis and drug-induced renal impairment, with glomerulonephritis being a rarer cause [92]. About 60% of instances with hallmark of renal involvement result in RA is glomerulonephritis [mostly mesangial], 25% are diagnosed with secondary amyloidosis, most frequent symptom in individuals with renal involvement and interstitial nephritis is infrequently seen [91,93]. This EAM may be a secondary effect of antirheumatic therapies, particularly NSAIDs and DMARDs [93]. In addition, the disease's extended duration and poor response to treatment are significant risk factors for this EAM [91]. Rituximab is a promising option for this illness; however, intense antirheumatic treatment currently yields a more favorable result [6].

Conclusion

The growth of the pharmaceutical sector with respect to RA has significantly benefited disease outcomes, and in turn, the prevalence of symptoms linked to long-standing comorbidities and chronic inflammatory responses has reduced. The care of systemic manifestations and problems, however, continues to be complex since progress has not been made equally in all areas and because several targeted medicines have led to the emergence of new difficulties. A general categorization of EAM in RA has not yet attracted a strong acceptance. A firm understanding on its definition, categorization, and administration should be necessary right now, especially in light of the variety of EAMs that are encountered in RA. In order to prevent, treat, and manage these consequences as well as to coordinate treatment among other healthcare professionals, rheumatologists are crucial. The pathophysiological mechanisms underlying the wide range of RA comorbidities are still being demonstrated in recent research. The incidence and morbidity of EAM are affected by the different RA therapy choices, and further research requires to understand this.

Acknowledgement

The authors would like to take this opportunity to express our gratitude and respectful thanks to all the faculty members who gave support and assistance for this review article.

Conflict of interests

All authors of this manuscript declare that this paper is void of any conflicts of interest.

Table 1: Extraarticular manifestations in rheumatoid arthritis, according to Malmö criteria[4]

Affected tissue/organ	Non-Severe EAM	Severe EAM
Skin	Nodules, Vasculitis Raynaud's phenomenon	Petechiae, purpura, ulcers, gangrene
Pulmonary system	Bronchiolitis obliterans Organizing pneumonia	Pleuritis Interstitial lung disease
Heart	Valvular heart disease Myocarditis, Arrhythmias	Pericarditis Coronary vasculitis and aortitis
Nervous system	None identified	Mono/polyneuritis multiplex Central nervous system vasculitis
Eyes	Secondary Sjögren's syndrome Sicca syndrome	Episcleritis or scleritis Retinal vasculitides
Hematological system	Anemia, thrombocytosis	Felty's syndrome
Renal system	None identified	Glomerulonephritis, Interstitial nephritis Amyloid deposition
Musculoskeletal system	Osteoporotic changes, tendon, and ligament rupture	None identified

References

1. Harris ED. Clinical features of rheumatoid arthritis. In:Kelley's Text-book of Rheumatology,7th ed. Philadelphia, PA: W.B. Saunders; 2005:1043-1078
2. Minichiello E, Semerano L, Boissier M. Time trends in the incidence, prevalence, and severity of rheumatoid arthritis: A systematic literature review. Joint Bone Spine. 2016;83(6):625-630.
3. Gabriel S, Crowson C, Kremers H, Doran M, Turesson C, O'Fallon W et al. Survival in rheumatoid arthritis: A population-based analysis of trends over 40 years. Arthritis & Rheumatism. 2003;48(1):54-58.
4. Smolen J, Aletaha D, McInnes I. Rheumatoid arthritis. The Lancet. 2016;388(10055):2023-2038.
5. Firestein GS. Etiology and pathogenesis of rheumatoid arthritis. In:Kelley's Textbook of Rheumatology, 7th ed. Philadelphia, PA: W.B.Saunders; 2005:996-1042
6. Das S, Padhan P. An overview of the extraarticular involvement in rheumatoid arthritis and its management. Vol. 8, Journal of Pharmacology and Pharmacotherapeutics. Medknow Publications; 2017. p. 81–6.
7. Majithia V, Geraci SA. Rheumatoid Arthritis: Diagnosis and Management. Vol. 120, American Journal of Medicine. Elsevier Inc.; 2007. p. 936–9.
8. Guidelines for the management of rheumatoid arthritis: 2002 Update. Arthritis & Rheumatism. 2002;46(2):328-346.
9. Hurd ER. Seminars in Arthritis and Rheumatism Extraarticutar Manifestations of Rheumatoid Arthritis.
10. Turesson C, Jacobsson L, Bergström U. Extra-articular rheumatoid arthritis: prevalence and mortality. Vol. 38, Rheumatology. 1999
11. Cronstein BN. Interleukin-6--a key mediator of systemic and local symptoms in rheumatoid arthritis. *Bull NYU Hosp Jt Dis*. 2007;65 Suppl 1:S11-S15.
12. Bongartz T, Cantaert T, Atkins S, Harle P, Myers J, Turesson C et al. Citrullination in extra-articular manifestations of rheumatoid arthritis. Rheumatology. 2007;46(1):70-75.
13. Sahatçiu-Meka V, Rexhepi S, Manxhu-ka-Kerliu S, Rexhepi M. – Extra-articular manifestations of seronegative and seropositive rheumatoid arthritis. Bosnian Journal of Basic Medical Sciences2010; 10(1): 26-31
14. Mielants H, Van den Bosch F. – Extra-articular manifestations. Clin Exp Rheumatology 2009; 27(Suppl. 55): S56-S61

15. Turesson C. Extra-articular disease manifestations in rheumatoid arthritis: incidence trends and risk factors over 46 years. Annals of the Rheumatic Diseases. 2003;62(8):722-727.
16. Turesson C, McClelland R, Christianson T, Matteson E. Multiple extra-articular manifestations are associated with poor survival in patients with rheumatoid arthritis. Annals of the Rheumatic Diseases. 2006;65(11):1533-1534.
17. Bergström, U, Book C, Lin Y. Lower Disease Activity and Disability in Swedish Patients with Rheumatoid Arthritis in 1995 Compared with 1978. Scandinavian Journal of Rheumatology. 1999;28(3):160-165.
18. Yamamoto T. Cutaneous manifestations associated with rheumatoid arthritis. Rheumatol Int 2009 Jul;29(9):979-88.
19. Chen KR, Toyohara A, Suzuki A, Miyakawa S. Clinical and histopathological spectrum of cutaneous vasculitis in rheumatoid arthritis. Br J Dermatol 2002 Nov;147(5):905-13.
20. Magro CM, Crowson AN. The spectrum of cutaneous lesions in rheumatoid arthritis: A clinical and pathological study of 43 patients. J Cutan Pathol 2003 Jan;30(1):1-10.
21. B Prakash, Jayashankar C, VM S, SA B, K C. Cutaneous manifestations of rheumatoid arthritis. Internet Journal of Rheumatology and Clinical Immunology. 2015;3(1).
22. Ziff M. The rheumatoid nodule. Arthritis & Rheumatism. 1990;33(6):761-767.
23. Christian C. Rheumatoid arthritis: Etiology, diagnosis, management. Peter D. Utsinger, Nathan J. Zvaifler, George E. Ehrlich, editors. Philadelphia, JB Lippincott, 1985. 934 pages. Illustrated. Indexed. $67.50. Arthritis & Rheumatism. 1985;28(12):1440-1440.
24. Cojocaru M, Cojocaru IM, Silosi I, Vrabie CD, Tanasescu R. Extra-articular manifestations in rheumatoid arthritis. Maedica (Buchar) 2010; 5:286-91
25. Stevens MB. Rheumatoid nodules. In: Utsinger PD, Zvaifler NJ, Ehrlich GE, editors. Rheumatoid arthritis: etiology,diagnosis, management. Philadelphia: JB Lippincott Co; 1985.pp. 487-94.
26. Zuckner J. The progression of rheumatoid arthritis in re-lationship to prognostic factors. In: Utsinger PD, Zvaifler NJ,Ehrlich GE, editors. Rheumatoid arthritis: etiology, diagnosis,management. Philadelphia: JB Lippincott Co; 1985. pp. 309-16
27. Sayah A, English JC. Rheumatoid arthritis: A review of the cutaneous manifestations. Vol. 53, Journal of the American Academy of Dermatology. 2005. p. 191–209.
28. Bunim J, Ziff M, McEwen C. Evaluation of prolonged cortisone therapy in rheumatoid arthritis. The American Journal of Medicine. 1955;18(1):27-40.
29. Scott DG, Bacon PA, Tribe CR. Systemic rheumatoid vasculitis: a clinical and laboratory study of 50 cases. Medicine 1981;60: 288-97
30. Puéchal X, Gottenberg JE, Berthelot JM, et al. Rituximab therapy for systemic vasculitis associated with rheumatoid arthritis: results from the AutoImmunity and Rituximab Registry. Arthritis Care Res. 2012, 64:331-339.
31. Puéchal X, Miceli-Richard C, Mejjad O, et al. Anti-tumour necrosis factor treatment in patients with refractory systemic vasculitis associated with rheumatoid arthritis. Ann Rheum Dis. 2008, 67:880-884.
32. Golding JR, Hamilton MG, Gill RS. Arteritis of rheumatoid arthritis. Br J Dermatol 1965; 77:207-10
33. Mattey DL, Dawes PT, Fisher J, Brownfield A, Thomson W, Hajeer AH, et al. Nod-ular disease in rheumatoid arthritis: association with cigarette smoking andHLA-DRB1/TNF gene interaction. J Rheumatol 2002;29:2313–8.
34. England BR, Thiele GM, Anderson DR, Mikuls TR. In-creased cardiovascular risk in rheumatoid arthritis: mecha-nisms and implications. BMJ 2018;361:k1036.
35. Sen D, González-Mayda M, Brasington RD Jr. Cardiovas-cular disease in rheumatoid arthritis. Rheum Dis Clin North Am 2014;40(1):27–49.
36. Romano S, Salustri E, Ruscitti P, Carubbi F, Penco M, Giacomelli R. Cardiovascular and Metabolic Comorbidities in Rheumatoid Arthritis. Curr Rheumatol Rep. 2018;20(12):81
37. Skeoch S, Bruce IN. Atherosclerosis in rheumatoid arthritis: is it all about inflammation?. Nat Rev Rheumatol. 2015;11(7):390-400. doi:10.1038/
38. Corrao S, Sallì L, Arnone S, Scaglione R, Amat V, Cecala M, et al. Cardiac involvement in rheumatoid arthritis: evidence of silent heart disease. Eur Heart J Feb. 1995;16(2):253–6]

39. Ortega-Hernandez OD, Pineda-Tamayo R, Pardo AL, Rojas-Villarraga A, Anaya JM. Cardiovascular disease is associated with extra-articula manifestations in patients with rheumatoid arthritis. Clin Rheumatol 2009;28:767-75.
40. Voskuyl AE. The heart and cardiovascular manifestations in rheumatoid arthritis. Rheumatology (Oxford) 2006;45 Suppl 4:iv4-7.
41. Snyder MJ, Bepko J, White M. Acute pericarditis: diagnosis and management. Am Fam Physician. 2014;89(7):553-560
42. Kitas G, Banks MJ, Bacon PA. Cardiac involvement in rheumatoid disease. ClinMed 2001;1:18–21
43. Adler Y, Charron P. The 2015 ESC Guidelines on the diagnosis and management of pericardial diseases. Eur Heart J. 2015;36(42):2873-2874.
44. Imazio M, Bobbio M, Cecchi E, Demarie D, Demichelis B, Pomari B, et al. Colchicine in addition to conventional therapy for acute pericarditis: results of the Colchicine for acute PEricarditis (COPE) trial. Circulation. 2005;112(13):2012-2016.
45. Schwemmer S, Beer P, Schölmerich J, Fleck M, Straub RH. Cardiovascular and pupillary autonomic nervous dysfunction in patients with rheumatoid arthritis -a cross-sectional and longitudinal study. Clin Exp Rheumatol. 2006;24(6):683-689.
46. Chauhan K, Ackerman MJ, Crowson CS, Matteson EL, Gabriel SE. Population-based study of QT interval prolongation in patients with rheumatoid arthritis. Clin Exp Rheumatol. 2015;33(1):84-89.
47. Wilsher M, Voight L, Milne D, Teh M, Good N, Kolbe J, et al. Prevalence of airway and parenchymal abnormalities in newly diagnosed rheumatoid arthritis. Respir Med. 2012;106(10):1441-1446.
48. Olson AL, Swigris JJ, Sprunger DB, Fischer A, Fernandez-Perez ER, Solomon J, et al. Rheumatoid arthritis-interstitial lung disease-associated mortality. Am J Respir Crit Care Med 2011;183: 372–8.
49. Pinheiro FAG, Souza DCC, and Sato EI. A study of multiple causes of death in rheumatoid arthritis, The Journal of Rheumatology, vol. 42, no. 12, pp. 2221–2228, 2015
50. Bilgici A, Ulusoy H, Kuru O, Celenk C, Unsal M, Danaci M. Pulmonary involvement in rheumatoid arthritis. Rheumatol Int. 2005;25(6):429-435.
51. Baqir M, Ryu J. The Non-ILD Pulmonary Manifestations of RA. Lung Disease in Rheumatoid Arthritis. 2017;163-173.
52. Alunno A, Gerli R, Giacomelli R, Carubbi F. Clinical, Epidemiological, and Histopathological Features of Respiratory Involvement in Rheumatoid Arthritis. Biomed Res Int. 2017; 2017:7915340.
53. Grutters JC and Du Bois RM. Genetics of fibrosing lung diseases, European Respiratory Journal, vol. 25, no. 5, pp. 915–927, 2005.
54. Mori S, Koga Y, and Sugimoto M, Different risk factors between interstitial lung disease and airway disease in rheumatoid arthritis,Respiratory Medicine, vol. 106, no. 11, pp. 1591–1599, 2012.
55. Toyoshima M, Chida K, Suda T, Sato M. Methotrexate might increase mortality from interstitial lung disease in rheumatoid arthritis. Am J Respir Crit Care Med. 2012;185(9):1024-1026.
56. Perez-Alvarez R, Perez-de-Lis M, Diaz-Lagares C,Pego-Reigosa JM, Retamozo S, Bove A, et al. Interstitial lung disease induced or exacerbated by TNF-targeted therapies: analysis of 122 cases. Semin Arthritis Rheum. 2011;41(2):256-264.
57. Chatzidionisyou A and Catrina AI. The lung in rheumatoid arthritis, cause or consequence?, Current Opinion in Rheumatology, vol. 28, no. 1, pp. 76–82, 2016.
58. Assayag D, Lubin M, Lee JS, King TE, Collard HR, Ryerson CJ. Predictors of mortality in rheumatoid arthritis-related interstitial lung disease. Respirology. 2014;19(4):493-500.
59. Nurmi HM, Purokivi MK, Karkkainen MS, Kettunen HP, Selander TA, Kaarteenaho RL. Variable course of disease of rheumatoid arthritis-associated usual interstitial pneumonia compared to other subtypes. BMC Pulm Med. 2016;16(1):107
60. Wang JX, Du CG. A retrospective study of clinical characteristics of interstitial lung disease associated with rheumatoid arthritis in Chinese patients. Med Sci Monit. 2015;21:708-715
61. Young A, Koduri G. Extra-articular manifestations and complications of rheuma-toid arthritis. Best Pract Res Clin Rheumatol 2007;21:907–27.
62. Conforti A, Di Cola I, Pavlych V, Ruscitti P, Berardicurti O, Ursini F et al. Beyond the joints, the extra-articular manifestations in rheumatoid arthritis. Autoimmunity Reviews. 2021;20(2):102735.
63. Corcoran JP, Ahmad M, Mukherjee R, Redmond KC. Pleuro-pulmonary complications of rheumatoid arthritis. Respir Care. 2014;59(4):e55-e59.

64. Gotsman I, Goral A, Nusair S. Secondary spontaneous pneumothorax in a patient with pulmonary rheumatoid nodules during treatment with methotrexate. Rheumatology (Oxford) 2001; 40(3):350
65. Bongartz T, Nannini C, Medina-Velasquez YF, Achenbach SJ, Crowson CS, Ryu JH, et al. Incidence and mortality of interstitial lung disease in rheumatoid arthritis: A population-based study. Arthritis Rheum 2010;62:1583-91
66. Komarla A, Yu GH, Shahane A. Pleural effusion, pneumothorax, and lung entrapment in rheumatoid arthritis. J Clin Rheumatol 2015;21:211-5.
67. Chapman PT, O'Donnell JL,Moller PW. Rheumatoid pleural effusion: response to intrapleural corticosteroid. J Rheumatol
68. Gauhar UA, Gaffo AL, Alarcón GS. Pulmonary manifestations of rheumatoid arthritis. Semin Respir Crit Care Med. 2007;28(4):430-440.
69. Prete M, Racanelli V, Digiglio L, Vacca A, Dammacco F, Perosa F. Extra-articular manifestations of rheumatoid arthritis: An update. Autoimmunity Reviews. 2011;11(2):123-131.
70. Feist E, Pleyer U. Erkrankungen des äusseren Auges bei rheumatoider Arthritis [Diseases of the outer eye in rheumatoid arthritis]. Z Rheumatol. 2010;69(5):403-410.
71. Vignesh AP, Srinivasan R.Ocular manifestations of rheumatoid arthritis and their correlation with anti-cyclic citrullinated peptide antibodies. Clin Ophthalmol. 2015;9:393-397.
72. General E, Cantarini L & Selmi C. Ocular Involvement in Systemic Autoimmune Diseases. Clinic Rev Allerg Immunol 49, 263–270 (2015)
73. Doi.10.1007/s12016-015-8518-3
74. Tong L, Thumboo J, TanYK,Wong TY, Albani S (2014) The eye: a window ofopportunity in rheumatoid arthritis? Nat Rev Rheumatol 10(9):552–560. doi:10.1038/nrrheum.2014.
75. McGavin DD, Williamson J, Forrester JV, Foulds WS, Buchanan WW, Dick WC et al.Episcleritis and scleritis. A study of their clinical manifestations and association with rheumatoid arthritis. Br J Ophthalmol. 1976;60(3):192-226.
76. Artifoni M, Rothschild PR, Brézin A, Guillevin L, Puéchal X. Ocular inflammatory diseases associated with rheumatoid arthritis. Nat Rev Rheumatol. 2014;10(2):108-116.
77. Yoshida A, Watanabe M, Okubo A, Kawashima H. Clinical characteristics of scleritis patients with emphasized comparison of associated systemic diseases (anti-neutrophil cytoplasmic antibody-associated vasculitis and rheumatoid arthritis). Jpn J Ophthalmol. 2019;63(5):417-424.
78. McCluskey P, Powell RJ (2004) The eye in systemic inflammatory diseases. Lancet 364(9451):2125–2133. doi:10.1016/S0140- 6736(04)17554-5
79. Wakefield D, Di Girolamo N, Thurau S, Wildner G, McCluskey P (2013) Scleritis: challenges in immunopathogenesis and treatment. Discov Med 16(88):153–157.
80. Aoki H, Hiraoka M, Hashimoto M, Ohguro H (2015) Systemic cyclosporine therapy for scleritis: a proposal of a novel system to assess the activity ofscleritis. Case Rep Ophthalmol 6(2):149–157. doi:10.1159/000430490
81. Agrawal R, Lee CS, Gonzalez-Lopez JJ. Et al. Flurbiprofen: A Nonselective Cyclooxygenase (COX) Inhibitor for Treatment of Noninfectious, Non-necrotizing Anterior Scleritis. Ocul Immunol Inflamm. 2016;24(1):35-42
82. Suhler EB, Lim LL, BeardsleyRM, Giles TR, Pasadhika S, Lee ST, de Saint SA, Butler NJ, Smith JR, RosenbaumJT (2014) Rituximab therapy for refractory orbital inflammation: results of a phase 1/2, dose-ranging, randomized clinical trial. JAMAOphthalmol 132(5): 572–578. doi:10.1001/jamaophthalmol.2013.8179
83. Young S. – Ocular involvement in connective tissue disorders. Curr Allergy Asthma Res. 2005; 5: 323-6.
84. Brun JG, Madland TM, Jonsson R. A prospective study of sicca symptoms in patients with rheumatoid arthritis. Arthritis Rheum. 2003;49(2):187-192.
85. Bowman SJ. – Haematological manifestations of rheumatoid arthritis. Scand J Rheumatol. 2002; 31: 251-9.
86. Owlia MB, Newman K, Akhtari M. Felty's syndrome, insights and updates. Open Rheu- matol J. 2014; 8: 129–36
87. Goldberg J, Pinals RS. Felty syndrome. Semin Arthritis Rheum. 1980;10(1):52-65
88. ISSN : 14219662

89. Verhoeven F, Guillot X, Prati C, Wendling D. Treatment of pseudo Felty's syndrome: Is there place for rituximab?. Joint Bone Spine. 2015;82(3):196-199.
90. Balint GP, Balint PV. Felty's syndrome. Best Pract Res Clin Rheumatol 2004;18: 631–45.
91. Korpela M, Mustonen J, Teppo AM, Helin H, Pasternack A. Mesangial glomerulo-nephritis as an extra-articular manifestation of rheumatoid arthritis. Br J Rheu-matol 1997;36:1189–95.
92. Horak P, Smrzova A, Krejci K, Tichy T, Zadrazil J, Skacelova M. Renal manifestations of rheumatic diseases. A review. Biomed Pap Med Fac Univ Palacky Olomouc Czech Repub. 2013 Jun;157(2):98-104. doi: 10.5507/bp.2013.042. Epub 2013 Jun 7. PMID: 23752767.
93. Mielants H, Van den Bosch F. Extra-articular manifestations. Clin Exp Rheumatol 2009;27:S56-61.