Rheumatoid Arthritis: extra-articular manifestations and comorbidities

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Abstract

Although synovitis is the pathological hallmark of rheumatoid arthritis (RA), many extra-articular manifestations (EMs) and comorbidities likely occur due to the complex, chronic, inflammatory, and autoimmune features of RA. Cardiovascular (CV) disease is the most common cause of death in patients with RA. Compared to the general population, patients with RA have twice the risk of myocardial infarction and up to 50% increased CV mortality risk. Severe and prolonged disease activity, genetics, and inflammation (e.g. CRP, ACPA, cytokines, matrix-degrading enzymes) play important roles in CV disease and atherosclerotic damage. The second major cause of death in patients with RA is respiratory disease, which occurs in 30-40% of patients. RA may affect the lung interstitium, airways, and pleurae, while pulmonary vascular involvement is less frequent. Central and peripheral nervous system involvement is usually due to small vessel vasculitis, joint damage, or drug toxicity. There is also evidence that microvascular cerebral damage caused by systemic inflammation is associated with the development of Alzheimer's disease and vascular dementia. Some observational studies have hinted how Disease Modified Anti-Rheumatic Drugs and biologics could reduce the incidence of dementia. Primary gastrointestinal and renal involvements are rare and often relate to drug therapy. To minimize morbidity and mortality, physicians must manage RA disease activity (treat-to-target) and monitor risk factors and concomitant conditions (e.g. smoking cessation; weight regulation; monitoring blood pressure, lipids, thyroid hormone, folic acid and homocysteine; screening for depression, anxiety, atlantoaxial instability, and atherosclerosis). This article aims to provide an overview of the most prevalent and important EMs and comorbidities associated with RA.

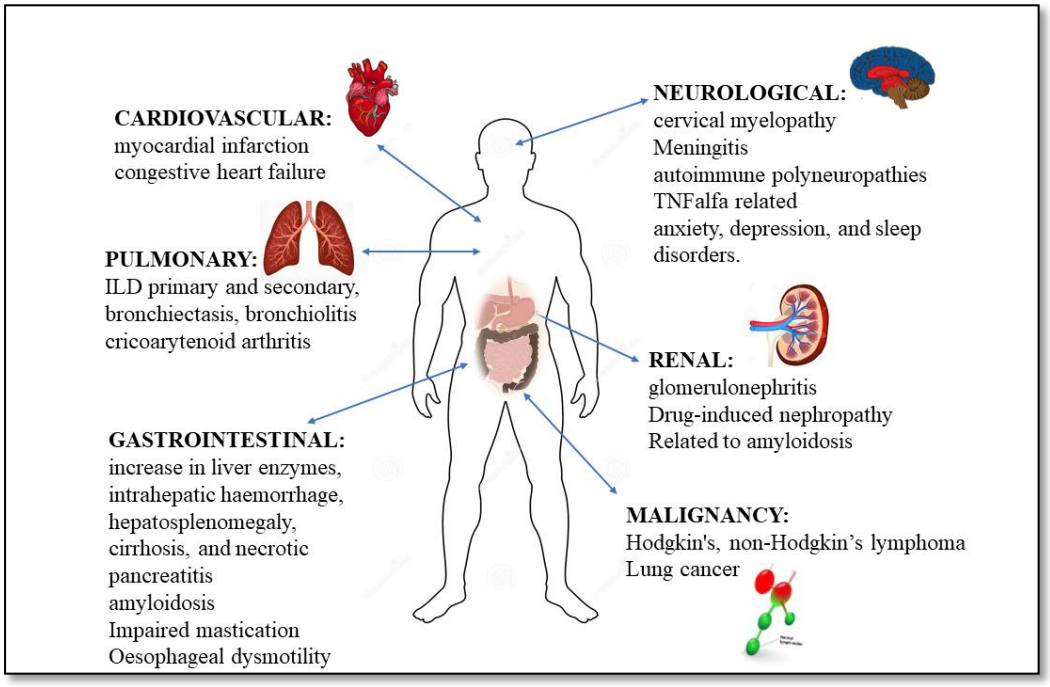
Keywords: rheumatoid arthritis, comorbidity, extra-articular manifestation, complications.

Introduction

Extra-articular manifestations (EMs) and comorbidities are frequent findings in rheumatoid arthritis (RA), leading to increased morbidity and premature mortality. The chronic inflammatory state of RA can lead to EMs such as rheumatoid nodules and vasculitis [1] as well as to cardiovascular (CV), pulmonary, neurological, gastrointestinal, renal, and hematologic disease [2] (figure 1). All RA patients should be screened for risk factors associated with EMs and comorbidities to prevent and manage severe complications. Evidence from the literature show that patient genetic characteristics and inflammation play a relevant role in the development of EMs and comorbidities and the disease control is crucial to prevent and limit their severity and the evolution towards serious events [1].

This review article aims to provide physicians with an overview of the most important EMs and comorbidities associated with RA.

Figure 1. The most frequent extra-articular manifestations and comorbidities of patients with rheumatoid arthritis.



Cardiovascular disease and chronic inflammation

Cardiovascular disease (CVD) is the most common cause of death in patients with RA. Studies have reported that patients with RA have twice the risk of myocardial infarction (MI) and up to 50% increased risk of CV mortality compared to the general population [3][4]. This may be explained only in part by an increased prevalence of known CV risk factors included in the Systemic COronary Risk Evaluation (SCORE), such as hypertension, hypercholesterolemia, diabetes, and smoking [5]. The links between the inflammatory processes of RA and atherosclerosis likely contribute to increased CVD risk [4].

The main clinical manifestations of CVD in RA are ischemic heart disease and congestive heart failure (CHF). In 2015, Mantel et al. compared 1135 RA patients with 3184 controls; they showed that patients with RA have more severe acute coronary syndromes and poorer outcomes after the attacks than the general population (HR= 1.50 [95% CI 1.19–1.90]), which can only be partially accounted for by the severity of the event [6].

Consistently with EULAR recommendations which state that adequate control of disease activity is necessary to lower the CV risk [5], a study in a large cohort of RA patients (24,989) followed for an average of 2.7 years showed a significant trend towards a reduced risk of CV events with improved RA control. There was a 21% reduction in CVD risk for every 10-point reduction of the Clinical Disease Activity Index (CDAI) (95% CI 13-29%) and a maximum of 53% CVD risk reduction from high disease activity to remission (95% CI 30-68%) [7]. Congestive heart failure (CHF) may occur twice as often in RA patients compared to the general population [8][9]. In 2016, Midtbø et al. demonstrated that higher disease activity in RA was correlated with lower left ventricular systolic myocardial function ($p<0.05$) independently of the presence of traditional CV risk factors like smoking, diabetes, and hypertension. Tight control of disease activity could help avoid CHF [10]. Notably, RA patients appear to have a more subtle initial CHF presentation that can delay diagnosis and treatment [11]. Among other CV manifestations, myocarditis, a disease related to CHF, has been reported in 11–50% of RA post-mortem analysis [12][8]. In contrast, cardiac complications such as pericarditis, endocarditis, cardiac tamponade, and long-term development of amyloidosis are rare.

CVD is a prime example of how the systemic inflammation of RA can impact an organ system outside of the musculoskeletal system. Other than traditional risk factors, inflammation in RA, characterized by an increase of specific inflammation indexes, cytokines, and antibodies, predisposes patients to

develop different comorbidities and contributes to the risk of mortality and disability. RA and atherosclerosis share many genetic and environmental factors that may cause endothelial dysfunction. An association has been found between endothelial dysfunction and HLA-DRB1*04 shared epitope (P = 0.01) [13]. Polymorphisms in loci outside the MHC regions appear to be associated with CV risk regardless of traditional risk factors [14][15]. Multiple markers of inflammation have been related to an increased cardiovascular risk, including erythrocyte sedimentation rates, C-reactive protein levels, number of joints affected, and disease activity and severity scores [16][17][18][19][20][21][22]. A high rheumatoid factor (RF) and anti-citrullinated protein antibodies (ACPA) serum levels are pathognomonic for RA and directly link RA and CVD risk. The circulation and deposition of immune complexes (CICs) produced by RF play a key role in the pathogenesis of vasculitis [23]. Moreover, ACPA is associated with a more aggressive RA course and with EMs [24]. A recent study by Twigg et al. on more than a thousand RA patients demonstrated that the comorbidities in ACPA-positive patients without inflammatory arthritis are the same as patients with early inflammatory arthritis [25]. This suggests that comorbidities in ACPA-positive patients may begin to appear before the onset of clinical signs of inflammation. In particular, ACPA positivity contributes to the development of CVD [25] and may induce subclinical atherosclerotic damage [26].

The inflammatory cellular infiltrates typical of synovitis also have many similarities to the inflammation contributing to arterial wall damage and atherosclerotic plaques (figure 2).

The same pro-inflammatory cytokines, matrix-degrading enzymes, and molecules have been deemed responsible for the onset and development of both synovitis and atherosclerotic vascular lesions [26]. The endothelium plays a central role because it produces vasoactive substances that act on the vascular tone and affects homeostasis between the circulating blood cells and the vessel wall. Nitric Oxide (NO) is one of the most important vasoactive substances. Inflammation can alter the balance between the production of NO and other vasoactive substances, causing endothelial dysfunction and consequently promoting atherosclerosis [27].

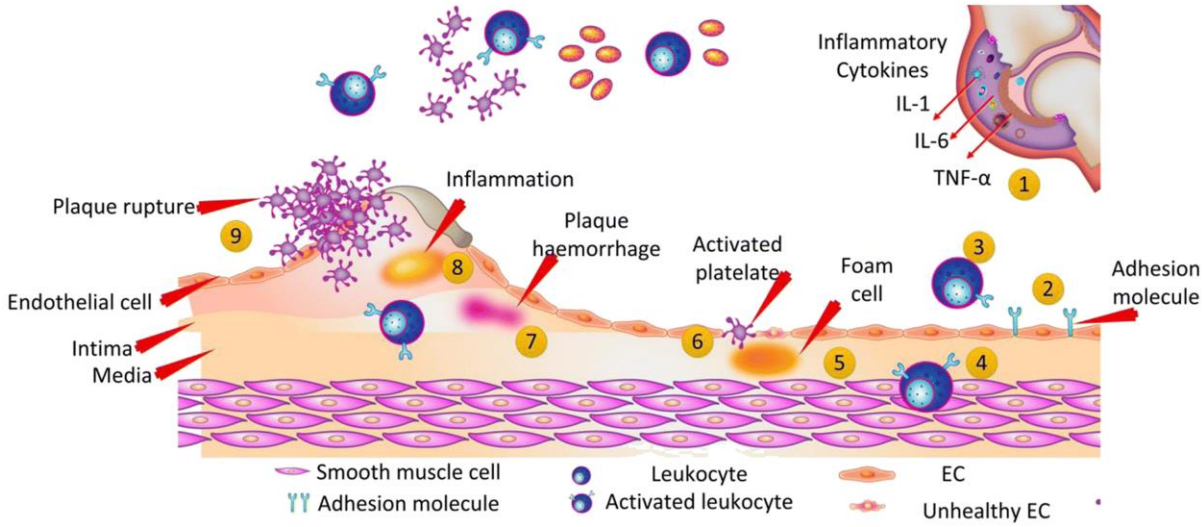


Figure 2. Mechanism of atherosclerosis driven by RA original authors from AtheroPoint™, Roseville, CA, USA (modified from [40] reprint license number 4860890636216)

Activation of endothelial cells by NO increases the endothelium permeability allowing low-density lipoprotein cholesterols (LDL-Cs) and immune cells, such as T-lymphocytes and monocytes, to enter into the subendothelial and intimal layer [28]. Monocytes get transformed into macrophages and take up oxidized LDL-C, transforming them into foam cells. Macrophages secrete pro-inflammatory cytokines such as IL-6 and TNF-α that recruit more lymphomonocytes within the intimal layer [28]. Cytokines such as TNF-α, IL-17, IL-6, and IL-1β are prevalent both in patients with RA and CVD [29]. These cytokines, which are involved in the development of the synovial pannus, also contribute to the activation of endothelial cells, initiating the atherosclerotic process. These molecules increase the coagulation cascade within the vessels and increase the rupture risk of atherosclerotic plaques. It is worthy to note that biologic and conventional DMARDs, effective in controlling RA disease activity, are also protective against atherosclerosis [30][31][32][33]. On the other hand, methotrexate decreases folate and increases homocysteine levels [34]. Low folate levels in RA patients may correlate with CVD risk. A recent study by Sonawane K. et al. evaluated the CVD and serum folate of 683 RA patients. They found that a serum folate level of at least 4.3 ng/mL was protective against CV mortality in patients with RA [35]. It may be useful to look for folate and/or homocysteine levels at the time of RA

diagnosis, especially when the patient's family history or past medical history is concerning for CVD. Close collaboration with cardiologists can be considered for the patients most at risk (i.e. with persistently elevated CRP, strong family history, or known CV pathology) to reduce acute events and prevent mortality.

In addition to specific cytokines, C-reactive protein (CRP) also correlates with impaired vasodilation and the extent of atherosclerotic plaque build-up. Higher levels of CRP are related to atherosclerosis, MI, CHF, and overall increased mortality [36] [37]. Furthermore, plaque vulnerability is greater in patients with active disease than in patients with inactive disease, linking plaque composition and inflammation [38][39]. Regardless of disease severity, however, RA patients without cardiovascular disease still display more coronary plaques that are more vulnerable than healthy controls (71% versus 45%) [38]. Carotid artery ultrasound is a non-invasive, economical, and efficient imaging approach that provides an atherosclerotic plaque tissue-specific image. Such images can help to morphologically characterize the plaque type and accurately measure intima-media thickness and wall variability. Machine learning and deep learning-based techniques may provide more accurate CV risk stratification for better management of RA patients [40] [41].

RA is also associated with a nearly two-fold increase in the risk of sudden cardiac death and cardiac arrest compared to the general population. This risk appears to be largely independent of conventional risk factors and highly related to systemic inflammation [42]. Recent findings suggest that long-lasting disease activity control may reduce ventricular arrhythmic risk in RA [42][43].

Additional risk factors for CVD, such as hypertension and diabetes, can be indirect consequences of RA. Several mechanisms contribute to the development of hypertension, including the use of anti-rheumatic drugs, the presence of specific genetic polymorphisms [44][44],and the activation of pathways that increase peripheral resistance [45]. In a cross-sectional study of 400 RA patients, 79.5% had hypertension and 39.4% remained untreated[46]. These statistics should make us reflect on the importance of managing common comorbidities. The association between insulin resistance and RA is supported by various studies that link inflammatory markers to disease activity [47][48] [49] [22]. While insulin resistance can lead to diabetes, the evidence correlating RA and diabetes is lacking [50]. Controlling inflammation with therapies such as anti-TNF alpha seems to reverse insulin resistance only in patients who are not obese, suggesting that weight regulation remains essential [51].

We must recognize the interdependence of organ systems affected by RA-related systemic inflammation. The inflammatory mediators common to RA contribute to CVD and illness throughout the body. Recognizing these consequences can help inform clinician action and mitigate the morbidity and mortality in the RA population.

Pulmonary manifestations

Respiratory system involvement occurs in 30-40% of RA patients, making it the second leading cause of death in patients with RA [52]. In 20-30% of them, a pulmonary complication is the first manifestation of their disease, preceding the joint symptoms [53]. For many others, the respiratory manifestations in RA occur within the first 5 years after diagnosis [54]. Mortality increases due to the susceptibility of RA patients to respiratory infections because of immunosuppressive drugs. Moreover, lung diseases may be asymptomatic, masked by a decline of general responses due to chronic inflammation, delaying diagnosis and treatment [55].

The pathophysiology of pulmonary disease in RA is not well known and is likely multifactorial. Recent studies correlate pulmonary involvement with genetic predisposition, smoking, chronic immune activation and dysregulation, environmental exposure, infection, drug toxicity, mucosal dysbiosis, and premature senescence [56][57]. Pulmonary diseases associated with RA primarily affect the lung interstitium, airway, and pleura, while pulmonary vascular involvement is less frequent. Interstitial lung disease (ILD) is the most common and severe manifestation of RA lung disease and is sometimes associated with parenchymal rheumatoid nodules. It is important to distinguish between primary ILD and secondary forms related to adverse effects of disease-modifying anti-rheumatic drugs (DMARDs), infections, or neoplastic disorders [58].

In a recent UK study, the relationship of pulmonary comorbidities to early mortality and joint damage was assessed in 6591 RA patients at the time of diagnosis and in the first 3 years of the disease course. The study showed that among the many comorbidities present in RA patients (asthma, chronic obstructive pulmonary disease (COPD), interstitial lung disease), COPD was the primary predictor of mortality within 3 years (HR 2.84, 95% CI 1.13–7.12; $P = 0.027$) [59].

Several studies also describe laryngeal involvement specific to RA patients. Arthritis of the cricoarytenoid joint, like other synovial joints, is characterized by synovial hypertrophy and joint

effusion leading to cartilage erosion and joint subluxation [53] [60]. Although cricoarytenoid arthritis is rare it is critical to recognize it to prevent and treat dysphagia, dyspnoea from exertion, glottal stenosis, and acute respiratory insufficiency (requiring urgent surgery) [53][61]. Finally, the pleural complications of RA include pleural thickening, effusions, empyema, nodules, pneumothorax, and trapped lung syndrome [62].

Gastrointestinal disorders

According to Kröner et al. [63], gastrointestinal tract involvement is frequently a direct consequence of RA or secondary to related autoimmune disease or ongoing therapies. The most common gastrointestinal comorbidity in RA patients is liver dysfunction, demonstrated by elevated liver function tests in 18-50% of patients with RA [64][65]. Other manifestations are intrahepatic haemorrhage, hepatosplenomegaly, cirrhosis, and necrotic pancreatitis [63]. Hepatic complications are often induced by drugs and related to fatty infiltration or non-specific reactive hepatitis with lymphocytic infiltration [66]. Moreover, Kim Su et al.'s recent retrospective study of 2812 RA patients found that increased liver fibrosis is an independent factor correlated to all-cause of mortality in RA patients – in addition to male sex, hypertension, diabetes, erythrocyte sedimentation rate, and intensity of glucocorticoid exposure [67]. Liver dysfunction is particularly common in Felty's syndrome, a subtype of RA typically characterized by splenomegaly and neutropenia. Approximately 75-95% of patients with Felty's syndrome present with hepatomegaly, regenerative hepatic nodular hyperplasia, peripheral lymphadenopathy, and rheumatoid nodules [68].

Impaired mastication can be due to temporomandibular joint RA or mouth ulcers and oral dryness (associated with Sjögren's or chronic inflammatory bowel disease). Oesophageal dysmotility can occur from concomitant connective tissue diseases, amyloidosis, or nerve compression during atlantoaxial subluxation. Rheumatoid vasculitis of small and medium vessels of the gastrointestinal tract affects 538% of RA patients, leading to intestinal bleeding or perforation, oesophageal or gastric ulcers, or appendicitis [23][63].

Another gastrointestinal complication occurring in up to 13% of RA patients is amyloidosis [63]. Any persistent inflammatory disorder can be complicated by amyloidosis. Chronic infections and inflammatory arthritis are the most common causes of amyloidosis in the developing and developed

world, respectively [69]. In RA, the development of amyloidosis seems more related to the duration of the disease than to its severity [70]. Acute manifestations are rare but can be very serious. Amyloid deposits in the liver and spleen can lead to organ rupture and urgent surgical intervention [71]. Amyloid deposits in the gastrointestinal tract can cause acute obstruction or significant bleeding. Depending on the location in the intestine, amyloid can also cause abdominal pain, nausea, malabsorption and chronic diarrhoea [72].

Neurologic involvement

RA can affect both the central and peripheral nervous systems. Neurological clinical manifestations may remain undetected or be falsely attributed to arthritic pain and dysfunction, causing diagnostic delays [73]. The involvement of the central nervous system is most often due to cervical myelopathy after atlantoaxial subluxation. Atlantoaxial involvement occurs in 43-86% of RA [74][75]. The formation of an erosive pannus in the articulation between the first and second cervical vertebra can cause bone destruction, laxity of the transverse ligament, and vertebral instability [76]. The subluxation can be anterior, posterior, or rotatory. The anterior atlantoaxial subluxation is the most common subtype, with a prevalence of 10-55%. The wide range is due to the variability in the radiographic definition of anterior subluxation [76]. The severity of cervical involvement is correlated to RA disease activity and duration; however, cervical involvement is asymptomatic in half of patients. The clinical presentation is variable: from acute, insidious, or chronic. Those with symptoms experience occipital headaches, vertigo, alterations in proprioception [74], visual and sensory deficits, and paresis. Possible serious consequences, such as vertebrobasilar insufficiency or brainstem compression, have a one-year mortality rate of 50% if not treated early [76]. Therefore, it is important to screen for cervical involvement, even in asymptomatic cases, to prevent neurologic injury and deficit [74].

MRI is the gold standard and preferred technique to evaluate the nerves, joints, and ligaments of the cervical region[77]. For clinical evaluation, Ulutatar proposed a method called the cervical joint position error test (CJPET) to evaluate proprioception (linked to atlantoaxial joint mechanoreceptors). All 106 RA patients tested significantly higher on CJPET than the matched healthy controls. The CJPET score was independent of neck pain, and a higher score was correlated to balance dysfunction and atlantoaxial subluxation on cervical radiography [74]. Other rare conditions affecting the cervical spine

that must be ruled out in symptomatic cases include infections or crystalline arthropathies (especially CPPD) [77]. A recent meta-analysis reported a significant reduction of anterior atlantoaxial subluxation prevalence in the last 50 years, probably due to the improvement of disease control with modern DMARDs [76].

Another pathology connected to RA is Alzheimer's disease (AD). Multiple studies highlight the role of chronic inflammation in the development of microvascular brain damage, microglial activations, and dementia [78] [79][80]. AD patients show elevated serum levels of pro-inflammatory mediators (TNF-alfa, IL1, IL6)[78][81], and many observational trials suggest that the use of TNFi and csDMARDs could reduce the risk of developing AD [78].

A rare but very serious neurological manifestation of RA is meningitis of the brain or spinal cord [2]. A recent publication reported that rheumatoid meningitis occurs almost exclusively in patients with a long history of seropositive arthritis, even when the disease is in remission [82]. Patients with rheumatologic meningitis as a presenting feature of RA are very rare [83]. The clinical manifestations of meningitis can be headache, neuropathy, stroke-like symptoms, disorientation, impaired consciousness, hydrocephalus, and dementia [82]. Another dangerous neurological complication of RA is transverse myelitis. This acute inflammation of the spinal cord can present insidiously with lower back pain, leg pain, bladder dysfunction, and autonomic anomalies that rapidly progresses to paraplegia [84].

RA drugs are well-known causes of neurological side effects. Among the adverse effects of non-steroidal anti-inflammatory drugs, neurological events including psychosis, cognitive dysfunction and aseptic meningitis are more common in elderly patients, especially with the use of indomethacin [73]. Methotrexate can cause headaches, fatigue, and impaired concentration. The use of cyclosporine can cause symptoms ranging from tremor, headaches, changes in mental function, and convulsions to the more serious complications of reversible posterior leukoencephalopathy [73]. Moreover, studies describe a correlation of anti-TNF treatment with the paradoxical development of autoimmune polyneuropathies, such as Guillain Barré syndrome, chronic inflammatory demyelinating polyneuropathy, and multifocal motor neuropathy. The hypothesis on the pathogenesis of anti-TNF's neurotoxicity involves both T-cell and humoral immunity against the myelin of the peripheral nerves in conjunction with vasculitis-induced nerve ischemia [73].

Finally, RA can be associated with mood disorders, such as anxiety, depression, and sleep disorders. The prevalence of depression in patients with RA is 13-20%. Anxiety exists in 21-70% of patients [85][86]. The presence of functional disability, pain, fatigue, and reduced quality of life play an important role in the development of mood disorders. Though the precise pathophysiological mechanisms remain nebulous, a recent study showed a correlation between disease duration, disease activity, CRP levels, and the presence of anxiety and depression [85]. Pu et al. also found that vitamin D deficiency is more prevalent in RA patients with depression and anxiety [85]. Vitamin D has neuroprotective properties through its action to prevent oxidative stress in the central nervous system, and deficiencies could contribute to mood disorders.

Renal disorders

Until a few years ago, glomerulonephritis was the most common renal disorder in RA [87]. Mesangial or membranous glomerulonephritis and minimal change nephropathy are possible EMs of RA. Nowadays, renal disease is more commonly related to complications of RA drug therapy and less frequently to amyloidosis [88]. Drug-induced nephropathy is mainly related to the use of NSAIDs and conventional DMARDs, such as methotrexate. More recently it has been linked to biologics therapy. Since the first report of 2 RA patients treated with anti-TNF alpha developed glomerulonephritis by Kemp et al. [89], several additional cases of paradoxical autoimmune renal involvement after biologic therapy have been reported. Autoimmune renal disorders induced by biologics is rare, reported in 0.9 cases per 1000 patient-years, but clinicians should be aware of this potentially life-threatening event [90].

Malignancy

Studies support that RA has a modestly higher overall incidence of malignancy compared to the general population [91]. A recent meta-analysis reconfirmed the association between RA and some malignancies, concluding that patients with RA have an increased risk of Hodgkin's disease, non-Hodgkin’s lymphoma, and lung cancer, but a reduced incidence of colorectal and breast cancer. Prostate cancer, cervical cancer, and melanoma seem to trend with the general population [91]. It has been proposed that continuous immunological stimulation in RA may increase the risk of malignant

transformation of the immune system and decrease the number of T-suppressor lymphocytes, thereby increasing the incidence of Hodgkin's lymphoma. Moreover, chronic pulmonary inflammation (especially in combination with smoking) can increase the incidence of lung cancer. For both Hodgkin's lymphoma and lung cancer, the increased risk was associated to the autoimmune pathogenesis of RA, genetic factors, and viral infections [91]. In contrast, the use of NSAIDs (frequently taken by RA patients) can reduce the risk of colorectal cancer [92]. Thankfully, many randomized controlled trials and a recent meta-analysis have shown that there is no association between the use of biological therapies and the onset of tumours [93][94][95].

Conclusions

Extra-articular manifestations of RA affect all aspects of a patient's organ systems and life. Some of the most common and preventable comorbidities include CVD, pulmonary disease, gastrointestinal disease, and neurological disease. Early awareness and screening for concomitant conditions by physicians and close management of disease activity (treat-to-target) is crucial to minimize morbidity and mortality. A multidisciplinary approach is suggested as it improve the management of RA patients. Recent studies continue to illustrate the pathophysiological mechanisms contributing to the broad spectrum of RA comorbidities. Future studies are needed to understand how the various RA treatment options affect the incidence and morbidity of EMs.

The manuscript does not contain clinical studies or patient data.

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TAKE HOME MESSAGE
• Rheumatoid Arthritis is associated with multiple extraarticular manifestations and comorbidities. • A multidisciplinary approach may improve the management of patients with rheumatoid arthritis. • Monitoring risk factors and treating comorbidities are crucial for an optimal disease management (e.g. smoking cessation; weight regulation; monitoring blood pressure, lipids, thyroid hormone, folic acid, and homocysteine; screening for depression,

anxiety, atlantoaxial instability, and atherosclerosis).

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