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Chapter

Vascular Involvement in Rheumatoid Arthritis

Alexandru Caraba, Stela Iurciuc and Mircea Iurciuc

Abstract

Rheumatoid arthritis (RA) represents the one of the most common inflammatory rheumatic diseases, which generates disability and significantly reduces the quality of life. RA can affect the vascular system, in addition to joint involvement. Vascular involvement increases the morbidity and mortality among these patients. Macrovascular disease, related to accelerated atherosclerosis, has a high prevalence among RA patients, in the form of carotid artery disease, ischemic heart disease, and peripheral arterial obstructive disease. Microvascular disease, studied in recent years by means of nailfold capillaroscopy, is present even in the early stage of RA evolution. Rheumatoid vasculitis can occur in severe forms of RA.

Keywords: macrovascular, microvascular involvement, rheumatoid arthritis

1. Introduction

Rheumatoid arthritis (RA) is a chronic inflammatory disorder, characterized by synovitis of small- and medium-sized joints, which causes cartilage breakdown, bone erosions, and finally destruction and loss of joints function. But beside the joints involvement, RA, especially with long-term evolution and suboptimal control of the disease activity, can generate systemic involvement (cardiovascular, respiratory, haematologic) [1].

RA is the most common inflammatory rheumatic disease, affecting about 0.5–1% of North American and European people over 18 years. The RA incidence and prevalence have regional differences: the lowest rates are identified in Southern regions, and the highest rates are present in Northern Europe and North America. Women are more frequently affected than men (women/men ratio 3/1), this disease occurring more commonly in the 4th or the 5th decades of life [2, 3].

RA is an autoimmune disorder; through the interaction between genetic predisposition and environmental factors, a trigger event generates an inflammatory autoimmune response, which affects primarily the synovial joint but also the blood vessels [1].

The interrelation between RA and vascular involvement began to be studied many years ago. In 2008, in their review, Szekanecz and Koch introduced the term "vascular rheumatology," referring to vascular impairment from inflammatory rheumatic diseases [4]. Indeed, in RA, vascular involvement comprises both macro- and microvessels. Special attention requires rheumatoid vasculitis, a rare but severe complication of this disease. Histologically, vascular lesions have been found in 25% of RA patients [5]. Patients with RA are prone to early and accelerated atherosclerosis, which induces higher cardiovascular risk, independent of traditional risk factors

(diabetes mellitus, arterial hypertension, smoking, dyslipidemia, age, lifestyle). RA-related risk factors are identified and characterized in these patients [6, 7]. In RA patients, the cardiovascular risk is obtained by the multiplication of measured risk (SCORE, Framingham) by a factor of 1.5, if two of the three following criteria are fulfilled (RA evolution >10 years, positivity of RF or ACPA, extra-articular involvement) [8].

2. Risk factors for vascular involvement

Vascular involvement in RA patients has a multifactorial model. Traditional cardiovascular risk factors together with those related to RA contribute to the development of macro- and microvascular involvement. It is known that the first step in atherogenesis development is endothelial dysfunction. Several factors associated with RA are involved in the endothelial dysfunction appearance: pro-inflammatory mediators and cells, oxidative stress, insulin resistance, physical inactivity, genetic factors, and drugs [9].

During its evolution, RA is a chronic inflammatory condition. Even in the preclinical stage, then continuing with the period when the clinical picture is complete, the chronic inflammatory environment exists in these patients. Pro-inflammatory cytokines contribute to synovial inflammation and to atherosclerosis development, through endothelial dysfunction.

Under physiological conditions, endothelium represents an active barrier between vascular wall and bloodstream, being involved in maintaining vascular muscle tone and homeostasis, controlling cell adhesion, proliferation, and coagulation balance. In pathophysiological conditions (chronic inflammatory diseases), these endothelium physiological functions are disturbed, and endothelial dysfunction occurs. During this new situation, reduced vasodilation, pro-inflammatory and prothrombotic status, and increased cell adhesion and proliferation contribute to atherosclerosis development. Endothelial dysfunction is a preclinical marker of atherosclerosis development, commonly detected in RA patients, but it is also involved in plaque progression and the occurrence of atherosclerotic complications [10, 11]. In RA patients, endothelial dysfunction occurs differentially in different vascular beds (macro- and microcirculation) [12]. Bocci et al. showed that in RA patients, the coronary microvascular involvement is identified in the absence of macrovascular disease [13].

Several factors are involved in endothelial dysfunction appearance in RA patients (**Table 1**) [9, 11].

2.1 Arterial hypertension

High blood pressure represents an independent predictor of cardiovascular events in RA patients. COMORA study reported that the prevalence of high blood pressure among RA patients was about 40% [14]. In their meta-analysis, Baghdadi et al. reported that high blood pressure was associated with a relative risk of cardiovascular morbidity of 2.24 in patients with RA [15]. On the other hand, Panoulas et al. identified that the most important determinant of target organ damage in RA patients is arterial hypertension [16]. It is known that the increase in systolic blood pressure with 20 mmHg is associated with high risk of endothelial dysfunction and cardiovascular disease. Some drugs used in RA therapy, as Leflunomide, NSAIDs, corticoids, and cyclosporine, are associated with high risk of arterial hypertension development, with consecutive endothelial dysfunction [7]. In hypertensive RA patients, ambulatory blood pressure monitoring revealed that the non-dipper and excessive dipper

Traditional risk factors
• Arterial hypertension
• Dyslipidemia
• Insulin resistance and metabolic syndrome
• Obesity
• Smoking
RA-related factors
• Chronic inflammatory status
• Oxidative stress

Table 1.
Factors involved in RA endothelial dysfunction.

patterns were frequent among them and pulse pressure was increased, these characteristics predisposing to cardiovascular complications [17]. Most researchers wondered if high blood pressure is effectively controlled in RA patients. Panoulas et al. and Desai et al., in their studies, showed that the identification and effective control of high blood pressure is suboptimal in RA patients [18, 19]. Two studies published in 2016 and one published in 2019 showed that there were no significant differences in the diagnosis and therapy of high blood pressure in RA patients versus the general population [20–22].

2.2 Dyslipidemia

Dyslipidemia represents a well-known traditional cardiovascular risk factor, affecting between 55 and 65% of the RA patients [23]. These patients present low levels of low density lipoprotein (LDL), high density lipoprotein (HDL), and total cholesterol, these levels being inversely correlated with markers of inflammation. But during inflammation, these molecules develop functional and structural changes, becoming atherogenic and promoting endothelial dysfunction. Some drugs used in RA treatment may increase lipid levels: DMARDs, TNF-α inhibitors, tocilizumab, and IL-6 receptor blocker [8].

2.3 Insulin resistance and metabolic syndrome

The prevalence of insulin resistance and metabolic syndrome is increased in RA patients (40%), increasing the risk of endothelial dysfunction and cardiovascular events by twofold compared to the general population. RA with high activity increases the effect of insulin resistance/metabolic syndrome on endothelial dysfunction. The effect of the medication that decreases the RA activity (DMARDs, biologics) on insulin resistance is not to be neglected. Endothelial-dependent vasodilation, mediated by nitric oxide release, is impaired in insulin resistance individuals. They display high levels of endothelin and plasminogen activator inhibitor in plasma [8].

2.4 Obesity

Obesity, physical inactivity, and endothelial dysfunction coexist in RA patients. Obesity is associated with other cardiovascular risk factors, as atherogenic dyslipidemia, high blood pressure, insulin resistance, and low grade inflammation, generating endothelial dysfunction. But in RA an association between low body mass

(secondary to high rheumatoid inflammation, generating rheumatoid cachexia) and cardiovascular events, too, is described [8].

2.5 Smoking

Another cardiovascular risk factor, smoking, is involved in RA appearance [24]. Rojas-Serrano et al. showed that the RA patients who smoked had a more severe RA evolution and positivity for rheumatoid factor and anticitrullinated protein antibodies [25]. Baghdadi et al. demonstrated that the cardiovascular risk was higher in RA patients who smoked [15].

Baghdadi et al. revealed in their meta-analysis that in RA patients the increased cardiovascular morbidity is related to the presence of high blood pressure [relative risk (RR): 2.24, 95% confidence intervals (CI): 1.42–3.06], smoking (RR: 1.5, 95% CI: 1.15–1.84), obesity (RR: 1.16, 95% CI: 1.03–1.29), insulin resistance (RR: 1.94, 95% CI: 1.58–2.30), and atherogenic dyslipidemia (RR: 1.73, 95% CI: 1.03–2.44) [15].

2.6 Inflammation

Chronic inflammation is considered to be an independent risk factor for the atherosclerosis development. Together with immune dysregulation, it contributes to endothelial dysfunction and atheroma plaque development. The cardiovascular risk begins to be evident from the early stages of RA, making the cardiovascular investigation necessary even from the first medical visit [26].

Chronic inflammation is considered to be of utmost importance in endothelial dysfunction onset. The previous studies have shown that the inflammatory processes in the rheumatoid synovium and atherosclerotic plaques are remarkably similar. TNF-alpha, interleukin-1 (IL-1), and interleukin-6 (IL-6) play an important role in RA pathogenesis, but they are involved in the development of endothelial dysfunction, too. TNF-alpha increases IL-1, IL-6, IL-8, and chemokines synthesis. On the other hand, this cytokine increases cellular infiltration in the synovium, through enhancing chemokine expression, endothelial cells activation, and neoangiogenesis. IL-1 stimulates the expression of adhesion molecules on the endothelial cells and neoangiogenesis. IL-6 contributes to endothelial cell activation; upregulates the expression of the chemokines that attract T cells, leading to enhanced cellular infiltration; and increases the concentration of VEGF with high vascular permeability appearance. VEGF induces the endothelial cell activation and differentiation, generating neoangiogenesis, too. These cytokines have metabolic effects, acting on the adipose tissue, the skeletal muscle, and the liver and contributing to the traditional cardiovascular risk factor production (insulin resistance, obesity). They contribute to the endothelial dysfunction development.

The inflammatory environment increases the effect of traditional cardiovascular risk factors on endothelial cells, generating endothelial dysfunction development. Other studies revealed that the anti-inflammatory treatment improves the endothelial dysfunction in RA patients [8, 27, 28].

2.7 Reactive oxygen species

Reactive oxygen species (ROS), generated at higher concentrations at sites of inflammation, can induce cellular injury. Vascular endothelial cells represent the main target for the ROS, increasing the endothelial permeability and promoting leukocyte adhesion. On the other hand, high levels of ROS and low levels of antioxidants in RA with high inflammatory activity generate the impairment of the HDL

function. Through these effects, ROS contributes to the endothelial dysfunction appearance in RA patients [7, 10].

2.8 RA treatment and vascular dysfunction

The drugs used in RA therapy may contribute to vascular dysfunction and cardiovascular risk.

Nonsteroidal anti-inflammatory drugs (NSAIDs) represent a class of drugs frequently used by these patients. The data regarding the NSAID use and cardiovascular risk in RA patients remain controversial. Data from the Danish nationwide registry revealed that the increased cardiovascular risk related to the overall use of NSAIDs in RA patients was modest and even significantly lower than in non-RA subjects. Rofecoxib and diclofenac were the exception, being associated with increased cardiovascular risk [29]. It is recommended to use NSAIDs with caution in RA patients in the presence of cardiovascular risk factors or in the presence of ischemic cardiovascular disease [8, 9].

Corticosteroids contribute to insulin resistance, high blood pressure, and atherogenic dyslipidemia; all these factors are associated with endothelial dysfunction and subsequently appearance of cardiovascular events. But, on the other hand, by controlling inflammation, corticoids may reduce cardiovascular risk in RA patients. EULAR recommended the corticoid use at lowest dose possible (<7.5 mg Prednisone/day), for the shortest period of time [9].

Among disease-modifying drugs (DMARDs), methotrexate, sulfasalazine, and hydroxychloroquine are associated with the cardiovascular risk reduction. By controlling inflammation (decrease of pro-inflammatory cytokine level), methotrexate improves the endothelial function in RA patients. But this drug contributes to endothelial protection by means of induction of AMPK-regulated protective genes. Sulfasalazine interferes with platelet function. Hydroxychloroquine improves lipid profile and has antithrombotic effects, thus reducing the cardiovascular risk. Leflunomide and cyclosporine are associated with arterial hypertension.

By using biologics (anti-TNF-alpha, anti-CD28, anti-CD20, anti-IL 6, anti-IL1), cardiovascular risk was reduced comparatively with the RA patients without this therapy.

Anti-TNF-alpha therapy improves endothelial function by means of inflammation reduction. It is important to know that the reduction in cardiovascular risk was recorded only in patients responsive to anti-TNF-alpha treatment.

Anti-IL-6 therapy improves endothelial function (measured by means of flow-mediated vasodilation) very early during the treatment. This effect is determined by reducing inflammation, although total cholesterol, LDL-cholesterol, and triglyceride levels are increased.

Anti-CD20 therapy reduces RA activity and has favorable effects on lipid profile, reducing endothelial dysfunction.

The use of abatacept in RA treatment has generated conflicting data regarding vascular dysfunction. Tofacitinib increases total cholesterol levels but without change of atherogenic index. This new drug was associated with low rates of cardiovascular events in RA patients [1, 8].

3. Macro- and microvascular endothelial dysfunction

All these factors contribute to disruption of vascular environment at the macro- and microcirculation levels, occurring endothelial dysfunction [2, 7].

Morphological assessment	
Conducting artery	Carotid intima-media thickness (cIMT)
Capillaries	Nailfold capillaroscopy
Functional assessment	
Conduit artery	Pulse wave velocity (PWV) Pulse wave analysis (PWA) Flow-mediated dilation (FMD) Nitroglycerin-mediated dilation (NMD)
Arterioles	Laser Doppler imaging with iontophoresis Venous occlusion plethysmography

Table 2.
Methods for morphologic and functional vascular assessment.

Macrovascular and microvascular endothelial dysfunction is identified in RA patients, not associated with each other, increasing cardiovascular risk in these patients [30]. The studies revealed a weak correlation between microvascular and macrovascular endothelial dysfunction in RA patients. Microvascular endothelial dysfunction results from the interaction between inflammation, immune dysregulation, and traditional cardiovascular risk factors, representing a significant factor related to accelerated atherosclerosis and future cardiovascular events in RA patients [31].

Structural and functional assessment of vasculature in RA patients uses different methods (**Table 2**). It is known that the functional and morphological vascular changes may coexist, especially in the early atherosclerosis [27].

4. Macrovascular involvement in RA

Endothelial dysfunction is present in RA patients compared to healthy controls. Although not all studies have shown the connection between endothelial dysfunction and inflammation, the use of specific RA medication (especially anti-TNF-alpha) has improved endothelial function in RA patients [32].

Arterial stiffness is increased in RA patients compared with controls, but an association between arterial stiffness and disease activity was not highlighted [27, 32].

Most studies identified that the cIMT was increased in RA patients, even in cases with newly established diagnosis. cIMT increases with the disease duration but is well known that the increase of cIMT is associated with the age of patients. The most studies did not reveal a consistent link between inflammation and vascular parameters. Van Zanten et al. explained that the long-standing, not current inflammation has had vascular impact in RA patients [33]. Carotid plaque (**Figure 1**) is common findings among RA patients. Roman et al. reported that the carotid plaque was three times more prevalent in RA patients than in controls [34]. Dessein et al. identified that the 31% of RA patients had carotid plaque [35]. Another study, performed by Pope et al., reported a prevalence of carotid atherosclerotic plaque about 35% in RA patients [36]. Protogerou et al. highlighted the importance of carotid ultrasonography associated with the femoral one in RA cardiovascular risk assessment [37].

Plaque rupture leads to the occurrence of clinical events. The risk of plaque rupture is determined by its composition (calcification, lipid-rich necrotic core, neovascularization, inflammatory cell infiltration) and, on the other hand, by the

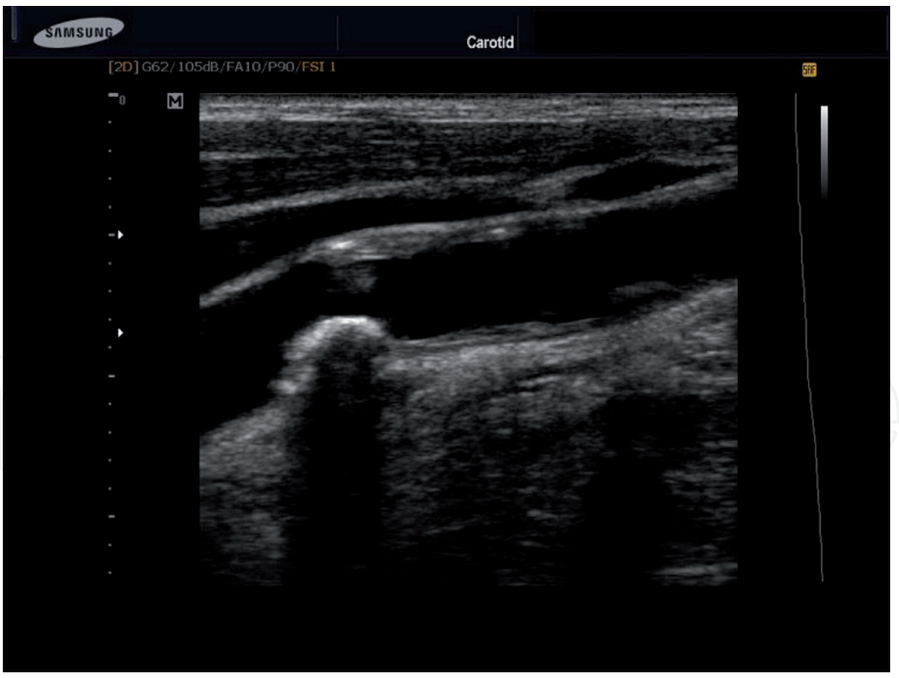

Figure 1.
Common carotid artery: Ultrasonography (increased cIMT and plaques in a long-standing RA evolution; personal collection).

presence of inflammation. Pro-inflammatory cytokines (IL-6, TNF-alpha) are related to plaque progression and the appearance of complications [32, 35]. Skeoch et al. demonstrated in their study the increased prevalence of atherosclerosis in RA, providing data to confirm that atheroma plaques are at high risk of complications [38].

Ruscitti et al. have shown increased incidence and prevalence of subclinical and clinical atherosclerosis in RA patients, but reaching and maintaining remission had positive effect on the atherogenesis development [39].

Further longitudinal studies are necessary in order to characterize the accelerated atherosclerosis in RA patients [32].

5. Microvascular involvement in RA

Yki-Jarvinen et al. studied the microvascular endothelial function in RA patients, using intrabrachial artery infusions of acetylcholine (endothelium dependent vasodilation) and sodium nitroprusside (endothelium independent vasodilation). The authors concluded that the basal blood flow was increased, correlated with the degree of RA inflammatory activity and more inhibited by NG-monomethyl-L-arginine, suggesting that the responsiveness to nitric oxide was reduced [40]. In another study, Galarraga et al. identified that the systemic inflammation (evaluated by serum levels of C-reactive protein) was independently associated with microvascular dysfunction in RA patients [41]. Studying 65 RA patients and 40 healthy controls, Arosio et al. showed that the RA patients presented impaired microcirculatory reactivity, endothelial dysfunction, and increased arterial stiffness. The authors concluded that these vascular alterations would be the link between RA and cardiovascular morbidity and mortality [42]. Endothelial dysfunction in RA patients was associated with high values of C-reactive protein and inducible nitric oxide synthase [43].

Microvascular morphological assessment may be performed by nailfold capillaroscopy, a noninvasive and repeatable method. By using this method, the following parameters are evaluated: tortuosity, loop size, density, angiogenesis, capillary loss, microbleeding, subpapillary venous plexus, and architectural structure [44].

McGill and Gow studied by nailfold capillaroscopy the microvascular changes in patients with systemic sclerosis (10 pts.), systemic lupus erythematosus (9 pts.), and rheumatoid arthritis (11 pts.). They reported that the nailfold capillaroscopy had a specificity of 89% and a sensitivity of 80% in the differentiation of the capillaroscopic models of these three diseases [45]. In another study, performed by Altomonte et al., the authors identified that in RA patients the common capillaroscopic changes were represented by elongation and capillary tortuosity. Besides them, the visibility of the subpapillary venous plexus was correlated with the endothelial dysfunction [46]. In the study performed on 80 RA patients and 30 healthy controls, Kuryliszyn-Moskal identified a significant correlation between soluble CD4 levels and the capillaroscopy findings [47].

In present, it is considered that there is no specific capillaroscopic model for RA [48]. Elongated and tiny loops, microhemorrhages, capillary low density, and subpapillary venous plexus visibility are common among RA patients [5].

Microvascular involvement appears early in the RA evolution. In their study, Scardina and Messina revealed that in patients with early RA, labial mucosa capillaries presented alterations, as: elongation, decreased capillaries caliber compared to healthy subjects. The authors suggested that the microvascular alterations could be extremely important in the diagnosis of suspected RA patients [5].

In their article, Lin et al. presented that in RA, the most common findings were represented by elongated and tiny capillaries and capillary tortuosity. The subpapillary venous plexus was visualized in RA patients who had antinuclear antibodies [44]. Sag et al. analyzed nailfold findings in 201 RA patients and 50 healthy controls. The authors examined the relationship between nailfold capillaroscopic findings and disease activity, expressed as DAS28. In 45.77% of RA patients, the authors identified nonspecific capillaroscopy findings: tortuosity, dilated capillaries, and bushy capillaries. The association of Raynaud's phenomenon increased the incidence of nailfold capillaroscopy abnormalities. No relation was found between microvascular abnormalities and RA activity score [49] (**Figure 2**).

Bernardino et al. identified mainly a non-scleroderma capillaroscopic pattern in RA patients. The authors suggested that the microvascular abnormalities identified in RA patients represented the results of inflammation and endothelial dysfunction [50]. Cutolo et al. highlighted that in RA patients "scleroderma-like" capillaroscopic pattern may be found, especially in association with rheumatoid vasculitis [51].

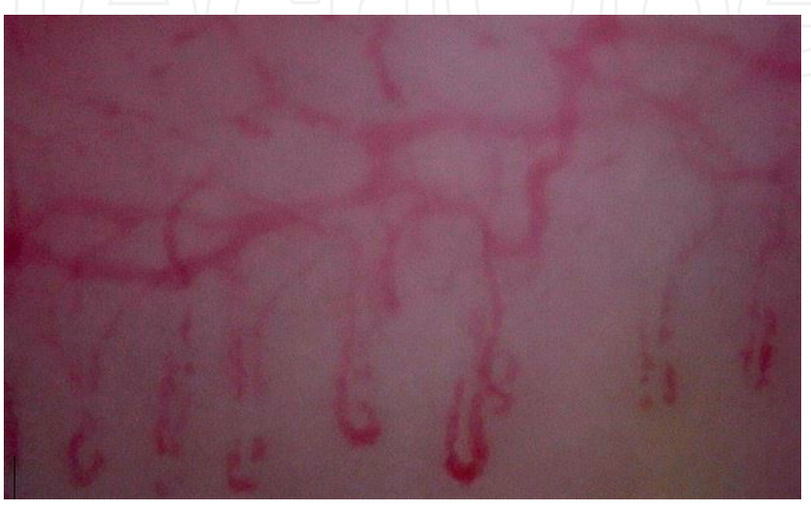

Figure 2.
Nailfold capillaroscopy (×200; subpapillary venous plexus visible, fragmentation of capillary blood circulation in patient with early RA; personal collection).

6. Rheumatoid vasculitis

Rheumatoid vasculitis (RV) is the most serious extra-articular complication of RA with long-term evolution, generating high rates of morbidity and mortality (up to 40%, during 5 years) [52].

It can affect any organ or system, but the most frequent involved are the skin (nailfold lesions, palpable purpura, and leg ulcers) and peripheral nervous system (mononeuritis multiplex, distal symmetric sensory or sensorimotor neuropathy) [53–55].

Due to earlier diagnosis and new therapeutic strategies for RA, the prevalence of RV had progressively reduced over time. RV appears in RA patients with severe immunological abnormalities, associating with other extra-articular manifestations [1].

RV is characterized by inflammation of small- and medium-sized arteries and capillaries. The risk factors associated with RV are represented by RA with prolonged evolution (> 10 years), rheumatoid nodules, males, smoking, seropositivity of rheumatoid factor, HLA-DRB1*0401/*0401, *0401/*0404, and *0101/*0401, HLA-C3 [55, 56].

RV can affect any organ or system of the body [1].

Clinical features of RV are cutaneous manifestations (digital infarcts, livedo reticularis, palpable purpura, ulcers, painful nodules, or even digital gangrene), peripheral nervous system manifestations (mononeuritis multiplex, distal symmetric sensory or sensorimotor neuropathy), and internal organ manifestations (due to coronary, cerebral, mesenteric, renal artery involvement, much less common, but with significant morbidity and mortality). The patients with Felty's syndrome develop more frequent RV [1, 54, 56].

Laboratory features of RV are represented by high levels of sedimentation rate and C-reactive protein, thrombocytosis, anemia, high levels of anti-cyclic citrullinated peptide antibodies and rheumatoid factor, and decreased levels of complement in patients with RV than the patients without this complication [1, 56, 57].

The RV diagnosis is easily established in the presence of cutaneous or nervous manifestations. Internal organ manifestations represent a challenge in establishing the correct RV diagnosis. Diagnosis confirmation is established by histopathological examination of the involved skin, muscle, nerve, or another affected organ [56].

In present, there are no guidelines for the RV treatment. Corticosteroids and cyclophosphamide have been used in severe, life-threatening cases of RV. In milder forms of RV, corticosteroids and methotrexate or azathioprine have been used. Rituximab and corticosteroids are preferred, due to higher efficiency and lower toxicity [55, 58, 59].

7. Conclusion

Vascular involvement in RA patients remains a chapter open to further research, in order to develop preventive measures, early diagnosis, and efficient therapy.

Conflict of interest

The authors declare no conflict of interest.

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