Rheumatoid Arthritis(RA)

Subjects: Biochemistry & Molecular Biology

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Rheumatoid arthritis (RA) is a chronic systemic autoimmune disease, which affects approximately 1% of the global population and occurs preferably in females, with a female-to-male ratio of 3:1. The disease can begin slowly and gradually with mainly non-specific symptoms such as fatigue, low-grade fever, general malaise, and joint pain; later, more defined symptoms such as intense pain, morning stiffness, and swelling of the joints have been described. In general, the joints most frequently affected are those of the hands and wrists, followed by those of the feet, knees, elbows, ankles, up to involving the wider joints of the shoulders, hips, jaws, and cervical spine. With overt disease, joint swelling occurs, caused by synovial effusion being associated to joint deformities and ankylosis. For this reason, RA is associated with a lower quality of life, a partial and/or total incapacity to work, a form of progressive disability and a higher probability of developing other co-morbidities.

Rheumatoid arthritis inflammation neurological extra-articular manifestations endothelial dysfunction

1. Extra-Articular Manifestations in Rheumatoid Arthritis

1.1. Multiorgan RA-Associated Disease

Patients with RA can develop a wide range of extra-articular manifestations (EAMs) and it seems they are caused by the involvement of genetic and immune factors [1]. In most cases, EAMs are accompanied by a process of vasculitis and a high titer of circulating Rheumatoid Factor (RF) and Anti-Citrullinated Protein Antibodies (ACPA) [2]. It has been shown that there is an increased risk of developing cardiovascular diseases in patients with RA and this percentage is about 50% higher than in healthy individuals [3]. The systemic inflammatory state present in RA can result in atherosclerotic damage, reduction of high-density lipoproteins, increased development of metabolic syndrome, and a state of hypertension [4][5][6]. In some instances, heart involvement may be asymptomatic and constitute a silent complication of RA [7].

Skin manifestations, which may occur in RA, include a wide range of diseases that have a significant negative impact on patients, on physical, emotional, and psychosocial well-being. For this reason, early recognition, understanding of these manifestations through an interdisciplinary approach, and adequate pharmacological treatment would be necessary in order to better manage this disabling condition. The major skin manifestations present in patients with RA may be rheumatoid nodules, granulomatous disorders, and neutrophilic dermatoses [8][9]. Rheumatoid nodules occur in 25–35% of patients with RA and have been associated with cardiovascular

disorders [10]. In addition, the skin of these patients may also present periungual infarctions, petechiae, purpura, or erythema. Again, in this case, skin manifestations are frequently preceded by necrotizing vasculitis involving medium-sized vessels[11].

Pulmonary involvement is a common EAM of RA and occurs in about 40% of patients [12]. These diseases can affect any of the lung compartments and can manifest as a complication of RA therapy, as an opportunistic infection, or as a result of a form of drug toxicity [13]. The most frequent manifestation is interstitial pneumonia, accompanied by documented widespread alveolar damage. In particular, the identification and management of these diseases requires the combination of histopathological and radiological clinical examinations [14].

Gastrointestinal manifestations, which occur in conjunction with RA, are rare but can have a very negative impact on patients. Some gastrointestinal processes are directly related to RA, while others may be consequences of pharmacological treatment of concurrent autoimmune diseases. In general, these manifestations are found in most patients with a particularly severe form of RA [15]. It concerns inflammatory processes against small vessels responsible for ischemic ulcers and perforations. The main symptoms include abdominal pain, nausea, diarrhea, and malabsorption [16]. Liver involvement is more rarely observed and is characterized by alteration of liver enzyme levels [17].

Patients with RA are normally accompanied by progressive damage to the joint bone and cartilage which is related to disability over time. The impact of inflammation on bone in RA is, in fact, particularly destructive and increases the risk of developing osteopotosis [18]. Patients with RA present a marked demineralization and erosion of bones. Inflammatory events are responsible for osteoclastogenesis and reduced osteoblastogenesis: inflammatory cytokines (tumor necrosis factor-α (TNF-α), interleukin-1 (IL-1), IL-6, IL-17) and immune cells negatively impact osteoblast differentiation and their ability to produce mineralized matrix [19]. For this reason and to improve the quality of life, it would be desirable for these patients to regularly monitor bone mineral density and undergo calcium and vitamin D supplementation [20]. In recent years, enormous progress has been made in the prevention of bone loss in the RA thanks to the advent of disease-changing agents, including biological agents and small molecules, which limit inflammation and can have a direct impact on the prevention of osteoclastogenesis. However, repair of existing bone erosion, although feasible, is rarely observed [21]. As new agents are introduced to control inflammation in RA and new mechanisms are identified to affect synovitis, it may be possible in the future to completely repair the damaged bone.

1.2. Neurological Disorders Associated to RA

EAMs that affect patients with RA are a wide range of neuronal damage. In particular, it has been highlighted that about 20% of patients can develop neuropathies, multiple mononeuritis, distal sensory neuropathies, and sensory-motor neuropathies. In all these disorders, neurological involvement occurs as a consequence of vasculitis of the nerve vessels leading to vascular ischemia, axonal degeneration, and neuronal demyelination [22]. Many neuropathies develop due to nerve compression, as in the case of carpal tunnel syndrome, generating not only pain but also paresthesia and neuronal damage. It has been shown that chronic synovitis, at the foot level, is

associated with the development of Morton neuroma and tarsal tunnel syndrome, two pathologies responsible for pain in patients with RA [23].

In addition to carpal tunnel syndrome, central nervous system involvement in RA patients includes multiple manifestations such as meningitis, optical atrophy, cerebral vasculitis, and rheumatoid nodule formation [24][25]. Among these alterations, cervical myelopathy is the most common in patients with RA for more than 15 years and is associated with significant morbidity and mortality [26]. The frequency with which cervical myelopathy occurs is 2.5% and the main symptoms are neck pain, occipital headache, sensory deficits, lower cranial nerve palsy, and transient ischemic attacks. These symptoms are caused by compression of the spinal cord and brain stem [27]. The cervical vertebrae C1 and C2 are the typical targets of the pathology and the involvement of the cervical spine can present various forms including erosions of the vertebral endplates, erosions of the spinous process, and changes in the apophyseal joint followed by osteoporosis [28]. These inflammatory lesions of the cervical spine, associated with frequent subluxations, occur within the first ten years after the diagnosis of RA, although many patients remain completely asymptomatic [29]. Diagnosis of cervical myelopathy is carried out by X-rays, through which it is possible to assess the parameters of the cranio-cervical junction. MRI also provides more detailed information on ligament structures [30]. Rheumatoid meningitis is a neurological manifestation of RA, affecting the central nervous system, which can occur during a remission phase of the autoimmune disease [31]. The main symptoms include headache, seizures, deafness, speech disturbances, and stroke-like symptoms, e.g., hemiparesis and cognitive impairment. Since these symptoms can be misinterpreted, it is necessary to make a correct diagnosis through the combination of numerous data including objective clinical presentation, analysis of the cerebrospinal fluid obtained by lumbar puncture, MRI of the brain, and a biopsy that can exclude other etiologies. Furthermore, to rule out possible infections, the cerebrospinal fluid should be negative [32]. The analysis of the pathological manifestations describes the chronic inflammation of the meninges, the concomitant presence of vasculitis, and necrotizing granulomas [33]. In some cases, but not all, the presence of ACPA and RF autoantibodies can be detected [34]. Rheumatoid nodules are nodular lesions found in the subcutaneous area normally subjected to pressure or mechanical stress, such as the joints of the fingers or forearm. They are usually present in about 20–40% of patients with more aggressive RA and the SPSA form; RF is, normally, present in patients with autoimmune disease who develop rheumatoid nodules. If, on the other hand, RF is absent it may be that the patients develop the other pathological forms [35]. Rheumatoid nodules are characterized by specific histological peculiarities: there are numerous macrophages and multinucleated cells arranged around a central necrotic area [36]. The presence of rheumatoid nodules reduces the functional capacity of the patient who is affected and a rehabilitation program is recommended. Sometimes, pharmacological and rehabilitative treatment is replaced by surgery, but this option has not always proven to be decisive [37]. In patients with RA, drug-induced toxicity is also involved in neuronal damage [38]: the scientific literature has highlighted that many extra-articular neurological manifestations present in RA could be due to adverse reactions of the common drugs taken for this autoimmune disease. Among these, it seems that prolonged use or high doses of glucocorticoids (GCs) can cause manifestations psychiatric and cognitive impairment . The use of Methotrexate, a drug widely used in RA, can cause peripheral neuropathies, retinal damage, and ear alterations [39]. Extra-articular neurological manifestations in RA also include the ophthalmological field; dry eye represents the most frequent occurrence of RA in the early stages of the disease and affects one in four patients.

Frequently, eye damage can worsen and turn into chronic conjunctivitis or corneal ulcers [40]. Inflammatory ophthalmological conditions include episcleritis, scleritis, and peripheral ulcerative keratitis and can greatly exacerbate ocular prognosis as they aggravate RA conditions and increase the risk of developing systemic vasculitis [41]. For this reason, at the time of the diagnosis of RA, there should be a close collaboration between the rheumatologist and the ophthalmologist. Scleritis, for example, when associated with RA, can lead to severe ocular complications and is thought to be caused by the deposition of the immune complex found in the necrotizing collagen associated with the sclera [42]. Scleritis in 40% of cases is bilateral and the necrotizing form is associated with an increase in the severity of RA; the characteristic symptom is represented by eye pain that greatly increases with eye movements [42]. Most cases of scleritis are treated with immunosuppressive drugs and have a good resolution, although some refractory cases are more aggressive and resistant to steroid therapies [43].

1.3. Cognitive Impairment in Rheumatoid Arthritis

Although neuropsychological damage is not usually associated with RA, recent studies have suggested the possibility of developing cognitive impairment, responsible for the alteration of daily life in patients with RA [44]. Cognitive function includes many neuropsychological domains, dealing with orientation, attention, concentration, judgment, problem-solving, memory, and visual-spatial conception [45]. More than 40% of patients with RA can generate neurological diseases, such as impairments on cognitive function, memory, verbal function, and attention alterations, and psychiatric symptoms such as anxiety and depression [46]. Current data have suggested that this cognitive decline may be due to prolonged inflammation in the brain or the high risk of cardiovascular comorbility responsible for, over time, the development of metabolic syndrome and increased inflammatory protein [47]. The cognitive impairment could also be associated with clinical characteristics (persistent pain, chronic fatigue, and sleep disorders) or with psychological comorbibities such as anxiety and depression [48]. The maintenance of cognitive function in patients with chronic diseases, such as RA, is extremely important to ensure successful performance in day-to-day activities and the management of pharmacological treatment schemes. An important clinical study was conducted in order to find the possible predictors of cognitive deterioration in patients with RA [49]. A number of physical, psychosocial, and biological parameters were included in this study. A third of patients with RA were cognitively compromised. It has also been shown that reduced education, lower income, concomitant use of glucocorticoids, and cardiovascular involvement were closely associated with high probability of cognitive impairment in people with RA.

2. The Impact of Lifestyle Changes in RA

Sixty percent of premature deaths could be attributed to unhealthy lifestyle that includes risk factors such as poor nutrition, cigarette smoking, alcohol consumption, obesity, and physical inactivity. Indeed, a healthy lifestyle has been associated with an estimated increase in life expectancy of 7.4–17.9 years in Japan, the UK, Canada, Denmark, Norway, and Germany [50][51]. Furthermore, it has been widely acknowledged that unhealthy lifestyles are the main risk factors for various chronic diseases and premature death [52]. In patients with RA, these risk factors are associ-ated with increase of morbidity and mortality [53]. Smoking has one of the strongest associations with poor health and it has many harmful pathological effects. However, its effects seem to depend on the quantity

and time of intake; for this reason, the cur-rent epidemiological evidence is difficult to interpret. Smoking of cigarettes and other tobacco products has become a risk factor for many diseases, particularly respiratory and cardiovascular. In addition, numerous studies have established an obvious rela-tionship between smoking and the onset of RA and stressed that smoking is the strongest known risk factor to develop RA [54]. It is also interesting to note that smokers have positive results for anti-RF and anti-ACPA autoantibodies both associ-ated with SPRA patients. Moreover, successive studies have evidenced that the rate of SPRA diminished as a result of the reduction or suspension of the smoke. SPRA and smokers have also shown a higher risk of X-ray progression and erosive disease than non-smokers. For these reasons, it would be desirable to advise patients with RA or even suspected RA to stop or reduce their exposure to smoking [55].

Physical exercise consists of a planned, structured, and repetitive set of move-ments with the aim of improving or maintaining physical fitness. The American Col-lege of Sports Medicine states that exercise is indisputably advantageous and, in healthy condition, should be an integral part of daily life, including cardiorespiratory training, endurance, flexibility, and neuromotor exercise [56]. The European League Against Rheumatism (EULAR) recommends similar behavior for patients with RA. Some clinical studies have highlighted the benefits of exercise interventions on aerobic capacity and an improvement in muscle strength in these patients [57].

Alcohol is a psychoactive substance that produces addiction and causes social and economic hardships, especially in heavy drinkers. It would be recommended that pa-tients with RA do not consume alcohol, since the main pharmacological treatments in-clude hepatotoxic substances and alcohol could interact and increase hepatotoxicity [58]. Another important reason justifying a recommended reduced alcohol consump-tion in RA is the indirect effects on bone tissue, which are related to the dose and dura-tion of consumption. While moderate consumption (1–2 drinks per day) does not ap-pear to be harmful to bone tissues, increased consumption could irreversibly damage bones and tendons [59].

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