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# **Extraskkeletal Manifestations in Rheumatoid Arthritis - Clinical Cases**

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## **1. Introduction**

Rheumatoid arthritis (RA) is a chronic, autoimmune disease, which attacks the joints but also may cause extra-articular complications. The disease can present itself in a variety of ways. It depends on many factors, including the presence of rheumatoid factor, presence and rate of anti-CCP, number of swollen and painful joints (over 20 in the beginning of the disease), levels of inflammatory markers (ESR, CRP), patient's young age, occurrence of rheumatoid nodules. Patients who present the above criteria, especially with early, polyarticular onset of the disease, have usually aggressive, progressive and destructive course of the disease manifested by extra-articular manifestations. Proper primary treatment in the early stage of RA may reduce the number of swollen joints and severity of inflammation, slow the progression of joint deformations and decrease the amount of erosions. However, it does not completely preserve the occurrence of extra-articular complications. A lot of these complications can be observed in patients with long lasting RA, with recurrent exacerbations, undertreated or non compliant. Many of RA symptoms can also be seen in other diseases. That is why the recognition of the disease in many times is difficult.

In this paper we provide overview of major extra-articular complications of RA, describing its incidence and clinical features. To illustrate the complexity, variety of course and most common diagnostic problems, descriptions of four case studies are also included.

## 2. Non joint related complications of rheumatoid arthritis

Because there is no agreed classification of complications accompanying RA, this paper includes not only extra articular manifestations but also non-articular complications of RA.

### 2.1. Rheumatoid anemia

Normocytic or microcytic anemia is a relatively common feature of RA. The development of anemia is related to the effects of proinflammatory cytokines: tumor necrosis factor alpha (TNF- $\alpha$ ), interferon gamma (IFN- $\gamma$ ), interleukin-1 (IL-1), and interleukin-6 (IL-6) [1].

Anemia in RA is a result of iron deficiency, related to increased hepcidin production, which is a recognized key factor of this disease. Hepcidin is a peptide hormone produced by the liver. It inhibits intestinal iron absorption, iron release from macrophages and hepatocytes and placental iron transport [2]. As a result, these mechanisms decrease iron delivery. The main mediator of hepcidin increase in inflammation is IL-6 [2]. The IL-6-dependent STAT-3 pathway and the unfolded protein response-associated cyclic AMP response element-binding protein-H (CREBH) pathway are responsible for the signal transduction pathways that regulate hepcidin during inflammation and endoplasmic reticulum stress [3].

Another factor regulating hepcidin level during inflammation is IL-1. It has been shown that hepatocytes can be stimulated directly by the cytokines IL-6, IL-1 $\alpha$ , and IL-1 $\beta$  to produce hepcidin [4]. Moreover, IL-1 induces hypoferrremia [5], up-regulates ferritin [6], and plays a primary role in the anemia of chronic inflammation [7].

It has been shown that increased TNF- $\alpha$  levels correlate with systemic iron deficiency [8]. Levels of TNF- $\alpha$  were found to be significantly higher in anemic compared to non-anemic patients [9]. TNF- $\alpha$  is a pro-inflammatory cytokine that decreases iron level through mechanisms that are independent of the induction of hepcidin [10]. Experiments with laboratory animals shown that treatment with TNF- $\alpha$  down-regulate mucosal transfer of iron [11]. Duodenal ferritin levels are induced in these animals, providing for iron storage during the acute phase response [12]. This mechanism would prevent dietary iron exsorption across the mucosa to circulation [13]. Treatment of macrophages with TNF- $\alpha$ , surprisingly is associated with a rise in intracellular free or labile iron that is required for activation of the transcription factor NF- $\kappa$ B [14]. NF- $\kappa$ B is an important regulator of cellular responses to stimuli such as stress. Reduction of intracellular iron by chelation has an inhibitory effect on NF- $\kappa$ B induction of TNF- $\alpha$  and other cytokines [15,16]. Further studies of the TNF- $\alpha$  mechanism are needed to better understand its reciprocal relationship with iron and control of the NF- $\kappa$ B inflammatory response [13].

It is considered that IFN- $\gamma$  can also modulate iron status. Recent In vitro studies suggest that IFN- $\gamma$  may modulate hepcidin induction by M. tuberculosis infected macrophages [17]. In vivo studies have shown that a high iron diet will reduce IFN- $\gamma$  [18], implicating its role in the deleterious effects that iron-loading can have on the immune response. IFN- $\gamma$  is a key modulator of macrophage iron status and immune functions [13]. In vitro studies show that IFN- $\gamma$  could induce nitric oxide production-mediated apoptosis process, which might be in-

volved in the pathogenesis of anemia in RA patients [19]. There is evidence suggesting that increased local IFN- $\gamma$  production in bone marrow may be implicated in the pathogenesis of anemia seen in up to 50% of patients with RA [20].

The best way of correcting anemia is to control systemic disease by treatment with disease-modifying antirheumatic drugs (DMARDs). It has been shown that treatment with infliximab and methotrexate significantly improves hemoglobin level among anemic RA patients when compared to treatment with placebo and methotrexate [21]. In trials of tocilizumab in RA substantial increase of hemoglobin levels was shown in patients with anemia in comparison to patients without the disease [22]. In patients with persistent anemia, an erythropoietin therapy may be considered. Erythropoietin therapy might be used if hormone level in serum is lower than 500 mU/ml [23].

## 2.2. Rheumatoid nodules

Rheumatoid nodules (RN) are the most common extraskeletal manifestations of RA. RN occur in approximately 20-35% of seropositive patients [24]. It does not depend on the severity of inflammation. Rheumatoid nodules usually appear in patient with long lasting and active inflammation process in RA (average disease duration of eleven years) [33]. However, 11% of patients have RN in early stage of the disease, sometimes even earlier than inflammation process in the joints. RN affects males more than females. Nodules are formed most frequently in soft tissues, skin colored, painless, movable. However, they can also be painful and attached to the structure below tendons and bursae. They gain size from 2 mm to a couple of centimeters in diameter. They appear in extensor parts of limbs in the proximal area of interphalangeal and metacarpophalangeal joints, proximal forearm, elbows, foots and ankles [25]. The nodules can occur not only subcutaneous but also internally – in lungs [26] and other internal organs (heart [27], liver [28], pancreas [29], kidney [30]).

In histopathology, rheumatoid nodules contain massive areas of sharply defined necrobiosis, specifically eosinophilic necrobiotic granuloma in the center, surrounded by a palisade of macrophages and fibroblasts, and a peripheral vascular area containing T lymphocytes and macrophages. Nodules have collagen degeneration and common fibrosis. Usually there are inflammatory components (tuberculoid and sarcoid reactions) [31]. Immunohistochemical studies of a rheumatoid nodules (RN) suggest that it is a Th1 granuloma with focal vasculitis. According to Hodkinson, patients with rheumatoid nodules have increased level of circulating Th1 and IL-12, IL-2, and VEGF levels and IL-8, than those without RN [32].

Etiology of RN is unknown, but there are series of studies suggesting that nodules are an effect of repeated trauma in the local tissue, which induce local vascular damage, and increase the level of proangiogenesis factors and cause granulation of tissue formations [32].

Nodules are usually asymptomatic but sometimes there is inflammation, ulceration, deeper nodules can have fistula. In this case a surgical and antibiotic treatment is required. Although RNs are a cosmetic issue and usually do not need medical treatment. Nodules can enlarge, recur or persist indefinitely. Sometimes nodules undergo remission after colchicine, hydroxychloroquine and D-penicillamine [34]. There are two (Ching et al. and Baan et al.)

double-blind randomized studies with corticosteroids injections and placebo [35,36]. Ching et al. injected 24 nodules in 11 patients and concluded that it is a safe and effective way of treating rheumatoid nodules [36]. Baan et al. has a similar conclusion. Surgical removal of the nodules may be considered if they limit joint motion [35].

### 2.3. Thrombocytosis

Thrombocytosis is one of the most common extra-articular manifestations of RA and is often correlated with the disease activity. Thrombocytosis is a manifestation observed in 40% of active patients with rheumatoid arthritis, it usually occurs during the active clinical stages of RA.

Thrombocytes or platelets are cytoplasmic fragments shed from mature megakaryocytes. These cells are implicated in the pathophysiology of a number of connective tissue disorders, including RA. Presence of platelets was documented in synovium [37] and synovial fluid of RA patients [38]. Activation of platelets in RA was observed in number of studies [39-42]. Platelet alpha granules contains number of biologically active substances, which released in response to activation, may contribute to the inflammatory cascade. Thrombocytes are a source of a number of substances e.g. P-selectin, platelet-derived growth factor, CTAP-III, acidic and basic fibroblast growth factor, epidermal growth factor, transforming growth factor beta, which may influence inflammation [43]. Positive correlation between P-selectine, platelets number and RA activity was observed [39].

Recent studies indicate that proinflammatory cytokines, playing a role in disease development, may have also megakaryocytopoietic/thrombopoietic properties [43]. Persistent overproduction of certain thrombocytopoietic factors can induce megakaryocytopoiesis and thrombocytopoiesis [44]. The megakaryocytopoiesis and inflammatory cascade of RA share hematopoietic cytokines and respond to a number of colony-stimulating factors. Progenitors of osteoclasts are important cells during the development of erosion [45]. Megakaryocytopoiesis – is a complex process of development of megakaryocytes from pluripotent stem cells. The process includes a number of events: cell division, endoreplication, abortive mitosis, and maturation which may result in the biogenesis of platelets [43]. Megakaryocytes and platelet production are dependent on the interactions of hematopoietic stem/progenitor cells, the bone marrow stromal microenvironment and intracellular events and are influenced by certain interleukins, colony-stimulating factors (CSF), and hormones which stimulate proliferation and differentiation at different stages [46]. Each day, approximately two hundred milliards of platelets are released into the circulation of healthy adults [43].

The main proinflammatory cytokines of RA, TNF- $\alpha$  and IL-1 $\beta$ , could contribute to the production of thrombocytes. Although not primarily involved in the production of thrombocytes in the marrow, TNF- $\alpha$  and IL-1 can influence on thrombocytosis during inflammation by inducing synthesis and secretion of megakaryocytopoietic cytokines (i.e. stem cell factor, granulocyte colony-stimulating factor, IL-6, IL-11, and leukemia inhibitory factor) [reviewed by 43]. Interleukin-1 is also a potent inducer of IL-6 megakaryopoiesis stimulatory cytokine [47].

IL-4 important anti inflammatory cytokine may also play dual regulatory role in thrombopoiesis of RA. It functions as a downregulator of megakaryocytopoiesis [48], but also interacts with other cytokines, costimulating the growth of hematopoietic precursors [49-51]. It was shown that IL-4 increases along with IL-1 and IL-6 in patients with active RA complicated by thrombocytosis [43, 52 and 53].

Roles of different pleiotropic megakaryocytopoietic cytokines have been investigated in patients with thrombocytosis secondary to RA. Among those cytokines, IL-6 predominates in the stimulation of megakaryopoiesis [54]. Moreover, IL-6 may be responsible for the higher TPO in inflammatory events [55]. IL-6 and thrombopoietin (TPO) may be responsible for the development of reactive thrombocytosis in RA [52, 53 and 56]. Thrombopoietin (TPO) is the main regulator hormone of platelet production. The binding of TPO to its receptor influences all stages of megakaryocyte development and thrombocytosis both in vivo and in vitro [57]. Enhanced megakaryocyte and platelet mass can act as negative feedback to the megakaryocytopoiesis via receptor-mediated uptake and catabolism of the TPO [57]. Therefore, TPO, proinflammatory cytokines, anti-inflammatory mediators, megakaryocyte mass, and platelets themselves act in concert to regulate megakaryocytopoiesis of RA. Platelets can also be activated, and the growth hormones secreted from their alpha granules may actively contribute to the tissue inflammation associated with RA [39-42].

#### **2.4. Pulmonary involvement**

Pulmonary involvement includes pleurisy/ pleural effusion, rheumatoid nodules, interstitial involvement, pulmonary vasculitis - pulmonary hypertension, airways involvement (obstructive bronchiolitis), drug-induced lung diseases.

Patients with RA have different prevalence of lung involvement. Estimated prevalence depends on the method of detection. For example, the incidence of lung involvement based on X-rays occurs in 1-12% of patients [58]. Next the functional test of lung capacity reveals 5-15% prevalence of restrictive lung disease [59]. However a reduction in the capacity of the lung to diffuse carbon monoxide was observed in more than 50% of the patients with RA [60]. The high-resolution computer tomography (HRCT) is the most sensitive detector of pulmonary changes in RA patients. The prevalence of lung involvement is up to 80% in RA patients [60].

Pleurisy/pleural effusion are the most common manifestations of the lung disease in RA. The prevalence is about 5- 20% of patients with rheumatoid arthritis [61]. The occurrence is significantly higher when considering postmortem studies - 40% - 75% [62]. Pleurisy appears in patients with active RA, more frequently in males than females. The amount of pleural effusion is usually small, and most of the patients do not require pleural puncture. The fluid is present over a couple of weeks. It resolves usually after corticosteroids therapy and DMARD's therapy. Sometimes when the amount of the fluid is high and the patient has symptoms of pulmonary insufficiency (short of breath, chest pain, cough) the thoracentesis is needed. Each time any infections and malignancy should be excluded in the first place.

Pulmonary rheumatoid nodules are usually coexisting with subcutaneous rheumatoid nodules and occur in patients with positive rheumatoid factor. Prevalence is different. It depends on a radiological method. Rheumatoid nodules are detected by X-ray in 0,2% of RA [63] patients and in 4% by HRCT [64]. Males are affected more often than females. Pulmonary nodules can be single or multiple, usually are asymptomatic. They appear in periphery right middle lobe or both upper lobes, gain from a couple of millimeters to a couple of centimeters in diameter [65]. In most cases a patient requires biopsy and malignancy exclusion. In histological examinations the pulmonary nodules look similar to the subcutaneous nodules. They are characterized by a central zone of fibrinoid necrosis, surrounded by a layer of palisading mononuclear cells within an outer zone of vascular granulation tissue, lymphocytes, plasma cells, and fibroblasts [66, 67].

In 1953 Caplan [68] described coexistence of rheumatoid nodules and pneumoconiosis in chest radiographs of coal miners suffering from RA. X-rays show that the nodules are about 0.5 centimeter up to a couple of centimeters in diameter, and also a massive fibrosis. Nodules can collapse or calcify [68]. The course of the disease is sudden, it can regress or progress. It develops especially in miners working in anthracite coal-mines and in people exposed to silica and asbestos [69]. Prevalence is higher among patients with silicosis. In Caplan's syndrome, a hypergammaglobulinemia with high level of alpha 2- globulin and a hypoalbuminemia may occur [70]. Unge et al. investigated thirteen cases of Caplan's syndrome by chest X-ray, rheumatic and immunological tests, heart and lung physiology and pathological-anatomical specimens. No positive correlation was found between exposure time to silica, radiological findings and the level of rheumatoid factor. There was also no correlation found between the degree of rheumatic inflammations and pulmonary progress. The hypothesis that silica acts as an adjuvant was not reflected in rheumatic parameters [71]. Patients with Caplan's syndrome require DMARD's therapy. In case of a progression in the lungs, the corticosteroid therapy is needed.

Interstitial lung disease is one of the lung manifestations in RA patients. According to the recent American Thoracic Society (ATS)/European Respiratory Society consensus classification, idiopathic interstitial pneumonias (IIPs) include seven clinico-radiologic-pathologic entities:

- idiopathic pulmonary fibrosis (IPF),
- usual interstitial pneumonia (UIP),
- nonspecific interstitial pneumonia (NSIP),
- cryptogenic organizing pneumonia,
- acute interstitial pneumonia,
- respiratory bronchiolitis-associated ILD,
- desquamative interstitial pneumonia,
- lymphoid interstitial pneumonia[72]

Hyun-Kyung Lee et al. performed a retrospective study at Asian Medical Center to investigate the histopathologic patterns of interstitial lung diseases in patients with RA and their correlation with clinical features and outcome [73]. UIP was the most common (55.6% in 10/18 patients) of the lung involvement in RA patients. NSIP was second popular (33.3% in 6/18). UIP was determined as fibrosis (fibrotic lesion and honeycombing). NSIP was divided in 3 histopathologic subgroups. First group was distinguished with interstitial inflammation, second group, with both inflammations, and fibrosis, and third group, primarily with fibrosis. The UIP group had worse diagnosis than the NCIS group [73].

Clinical features of pulmonary fibrosis in RA patients are similar to those of idiopathic pulmonary fibrosis. 90% of pulmonary fibrosis patients have earlier joint diseases. Males with seropositive RA are more exposed than females [74]. Patients with pulmonary fibrosis in RA reveal both lymphocytic alveolitis and neutrophilic inflammation with or without pulmonary fibrosis in bronchoalveolar lavage (BAL). This study showed increased levels of CD4 and CD4:CD8 ratio in lymphocytic alveolitis [75].

The pathogenesis of pulmonary fibrosis depends on two types of factors – RA-independent and RA-associated. The RA independent factors are linked with tobacco usage and alpha-1 antitrypsin level. The RA-associated factors combine with genetical predisposition of HLA gene occurrence and the cytokines level, especially proinflammatory cytokines by alveolar macrophages, in particular TNF- $\alpha$  [76].

Patients with pulmonary fibrosis have a different course of the disease. Some cases have a slowly progressing disease, some have stable course, while others show a rapidly deteriorating process of the disease. Severe loss of pulmonary functions is rare [77].

Drug induced pulmonary involvement in patients with RA can occur after methotrexate therapy, gold salts, D-pecicilamine, sulfasalazine.

Methotrexate – pneumonitis (MTX pneumonitis) is not a common complication but a life-threatening one. The data about the prevalence of MTX pneumonitis in RA shows a great variation. Several retrospective and prospective studies have reported prevalence rates between 0.3% and 11.6% [78]. The methotrexate complications can occur with a dose of 7.5 mg per week, as early as 1 month after initiation of therapy, and as late as two years therapy [79]. The clinical presentation of methotrexate – pneumonitis is nonspecific. In general, patients have a nonproductive cough, dyspnoea, fever, pleuric chest pain. Physical examination often reveals bilateral inspiratory crackles. Laboratory findings may include mild leukocytosis or eosinophilia. The X-rays could be normal or could reveal interstitial lung diseases. The high resolution tomography (HRCT) reveals “ground glass”. The pathology of the methotrexate - pneumonitis is unknown. However a toxic drug reaction is suggested by the accumulation of methotrexate in lung tissue. Age, sex, cumulative or weekly dose of methotrexate and the disease duration, are not associated with the development of MTX-pneumonitis. Recent studies suggest 5 conditions that induce an increased risk of the development of MTX- complication: diabetes mellitus, hypoalbuminemia, rheumatoid pleuropulmonary involvement, previous use of disease-modifying agents (gold, sulfasalazine, or penicillamine), older age [79]. Patients who are suspected of MTX-induced lung toxicity should cancel methotrexate

therapy. Most of the patients improve without any other intervention, but in some cases the corticosteroid therapy is needed.

The treatment of interstitial fibrosis in RA is variable because of variable course of pulmonary involvement. Generally, high daily doses of steroids are beneficial in some patients. In some cases immunosuppressive (azathioprine or cyclophosphamide) agent should be added to steroid therapy. Raghu et al. reported a prospective double-blind, randomized, placebo-controlled clinical trial with azathioprine combined with prednisone in the treatment of idiopathic pulmonary fibrosis. This study shows the efficacy of azathioprine associated with prednisone and both the frequency and risk of side effects are lower than those of cyclophosphamide [80].

## 2.5. Amyloidosis

Secondary amyloidosis is potentially a life threatening complication of RA. The prevalence estimates from 7% to 26% in RA patients [81]. Amyloidosis is worldwide and prevalence depends on demographic location. For example, a study from Finland of the autopsy records of 1666 patients with RA revealed a prevalence of amyloidosis of 5.8% [82]. SAA1 gene polymorphism increases frequency of amyloidosis. The frequency of SAA1 genotype is higher among Japanese, Chinese, and white Australians than in other races. The frequency of SAA1 in Japanese is about 40% [83].

Amyloidosis is characterized by extracellular tissue deposition of fibrils that are composed of fragments of serum amyloid A (SAA) protein produced by hepatocytes. Secondary amyloidosis occurs during chronic inflammations. In developing countries secondary amyloidosis coexist with chronic, infectious diseases, tuberculosis, leprosy, bronchiectasis, chronic osteomyelitis, and chronic pyelonephritis. In industrialized countries, noninfectious diseases such as rheumatoid arthritis (23-51%), juvenile idiopathic arthritis (7-48%) and ankylosing spondylitis (0-12%) may cause amyloidosis [84, 85]. It occurs in patients with RA, who have long and very active aggressive course of disease. Amyloidosis is related to the acute phase of inflammation and elevated serum SAA1 level. SAA synthesis and secretion by hepatocytes is mediated by cytokines, mainly IL-1, TNF- $\alpha$  and IL-6 [86].

The diagnosis of secondary amyloidosis is based on histological examination of tissue from fat tissue, upper gastro intestinal duct or rectum. The most common presentation in amyloid is renal. Renal involvement in RA patient with amyloidosis is approximately 90% of all. Almost every patient with renal involvement has proteinuria. In some cases a renal insufficiency (high level of creatynina and low level of GFR) may appear. Amyloidosis is associated with the occurrence of nephrotic syndrome (proteinuria > 3.5 g, hypoalbuminaemia, vascular edema of lower limb). The amyloid can be present in spleen and liver. However, even severe damage of liver and spleen is usually asymptomatic. Heart involvement occurs in 10% patients with RA. This is shown as poor diagnostic factor.

Survival rate of patients diagnosed with amyloidosis in RA is approximately 4-5 years [87]. The clinical risk factors associated with a poor survival are: female gender, older age, reduced serum albumin, and increased serum creatinine concentration [88].

First aim in treatment of amyloidosis in RA is to decrease the level of serum amyloid A, by means of inflammation processes suppression. The effective DMARD's therapy and biologic therapy can cause decreased level of inflammation and reduce probability of amyloidosis. First drug therapy in amyloidosis is based on immunosuppressive agents (cyclophosphamide [89], methotrexate [90], and azathioprine [91]), which improve the prognosis. According to Nakamura et al. cyclophosphamide therapy is more effective than methotrexate therapy in secondary amyloidosis in RA patients [92]. Biologic agents (anti TNF- $\alpha$  therapy) and inhibitor IL-6 decrease the level of serum Amyloid A by decreasing the polymorphism SAA1 gene. T. Nakamura performed a study about efficacy of etanercept in patients with AA amyloidosis secondary to rheumatoid arthritis. The conclusion of this study is that etanercept is safe and effective even in patient on hemodialysis [93]. The latest Nakamura study proved that etanercept treatment was more effective than cyclophosphamide treatment [94]. Eprodisate is a new class of antiamyloid compounds for treating AA amyloidosis, which results in a significant delay in progression to hemodialysis or end-stage renal disease in AA amyloidosis [95].

## 2.6. Sjögren's syndrome

Sjögren's syndrome (SS) is a chronic autoimmune inflammatory disease that affects lacrimal and salivary glands causing mucous dryness [96]. The symptoms are related to diminished lacrimal and salivary gland function and frequently present with keratoconjunctivitis sicca, xerophthalmia, xerostomia, sialadenitis, cervical caries and infections. SS can cause also systemic manifestations. They are subdivided into nonvisceral (skin, arthralgia, myalgia) and visceral (lung, heart, kidney, gastrointestinal, endocrine, central and peripheral nervous system).

Sjögren's syndrome is called secondary SS (sSS) when it is associated with other autoimmune disorders such as scleroderma and RA [97]. Sjögren's syndrome definition was developed by the team of experts from Europe and America, "European American consensus group criteria" (EACG) that requires for recognition criteria:

- Subjective ocular symptoms: symptoms of dry eyes over 3 months, foreign body sensation in the eyes,
- Subjective oral symptoms: symptoms of dry mouth over 3 months, swollen salivary glands
- Objective ocular signs: Abnormal Schirmer Test (tears flow less than 5 mm in 5 minutes)
- Objective oral signs: unstimulated whole salivary flow less than 1.5 ml in 15 minutes, abnormal parotid sialography, abnormal salivary scintigraphy
- Positive histopathological examination of lymphocytic infiltration at salivary glands, at least one focus score,
- Positive antibody titers antiSSA/SSB.

The SS diagnosis requires a presence of one subjective symptom plus 2 of the 3 objective criteria [98].

The development of SS secondary to RA occurs on a different genetic background (HLA DR4). A distinct set of therapeutic responses suggest different pathogenetic processes [99, 100]. SS secondary to RA seems to be a complication of this disorder: the sicca syndrome is less serious, Ab to Ro/SSA and La/SSB are present less frequently and the evolution of SS is closely linked to that of RA. SS secondary to RA usually is subclinical and requires specific tests for its diagnosis [99, 101].

As the physiopathology of these two diseases is distinctive, it is possible to suggest that patients with RA and secondary SS have two different diseases [96]. In primary SS there is an important role of B cells and type I interferon [97,102] in contrast to the predominance of Th17 cytokines in RA [103]. It was suggested that decreased expression of TGF- $\alpha$ 1 observed in patients with SS secondary to RA might promote joint destruction [101]. The concentration of TGF- $\alpha$ 1 was significantly higher in patients with RA than in those with SS accompanying RA and in control group. The highest serum TGF- $\alpha$ 1 concentrations were found in patients with most severe joint damage, as evidenced by Steinbrocker stage. TGF- $\alpha$ 1 is cytokine that prevents inappropriate autoimmune responses [101].

The exact prevalence of sSS in RA varies considerably, depending on the definition of sSS, disease duration of RA and geographic region [102]. It has been demonstrated in Spain that patients with RA duration up to 10 years have had a prevalence of secondary SS of 17% and after 30 years it was as high as 25% [103]. Another study of early arthritis in the UK confirmed the dependence of the prevalence of sSS on disease duration [104], but this relationship was not confirmed in the study from Norway [105]. However, significant correlation was found between reduced salivary production and RA disease activity [105]. Geographical variation was shown in a comparative study between Greek and British RA patients, sSS was demonstrated in 43% and 17%, respectively [106]. The prevalence of sSS may reflect geographical factors, but could also be due to the range of anti-TNF therapy [101].

The high prevalence of dry eyes in RA patients without fulfilling the diagnostic criteria for secondary SS has been noticed by Fujita et al. [107] who found it in 90% of non-SS RA patients. In his study only 10% of patients had Secondary SS. The correlation between secondary SS and disease activity was also studied. It was found that RA activity had no significant correlation with the presence of dry eyes. However there was some correlation to patients diagnosed with secondary SS [106]. Antero et al. could not find a higher RA activity measured by DAS-28 in patients with secondary SS when compared to the ones without it during the studies of Brazilian population. Neither secondary SS occurrence, nor eye sicca subjective and objective findings have any relation to the disease duration [101]. The presence of sicca symptoms was high in the studied population, although only 24% of patients met the criteria of secondary SS [101]. Ocular symptoms of dryness were more common than oral ones in RA patients [101]. The impact of sSS on RA is illustrated by a twofold increased risk of non-Hodgkin's lymphoma compared to RA patients without sSS [108], and there is a tendency of increased mortality in RA patients with sSS compared to RA patients without sSS [109,110].

A therapy for the Secondary Sjögren's syndrome with RA can be divided into four separate areas. First is to manage the dryness in the eyes and mouth as well as the skin and other

mucosal surface. Next is to treat non-visceral manifestations such as arthralgia and myalgia, chronic fatigue syndrome. These symptoms are generally treated with salicylates, nonsteroidal agents, and hydroxychloroquine [111]. Patients with SS have a low tolerance of NSAIDs resulting from dysphagia, secondary to decreased saliva flow and increased frequency of gastro-oesophageal reflux disease. Usually patients with RA and SS use low doses of steroids and hydroxychloroquine to reduce arthralgia and myalgia. For visceral involvement, including vasculitic skin lesions, pneumonitis, neuropathy, and nephritis, corticosteroids are used with the dosage of 0.5 mg per one kilogram body mass. Drugs such as hydroxychloroquine, azathioprine, and methotrexate are used to help the corticosteroids [112]. Methotrexate seems to be more useful than azathioprine in Secondary Sjögren's syndrome with RA [113]. The biological agent used in SS is rituximab. The recent studies show a significant decrease in fatigue, however no significant changes in secondary endpoints assessing glandular manifestations (unstimulated salivary flow rate and Shirmer's test results) [114, 115]. For life-threatening complications the cyclophosphamide therapy is needed. Lymphocytic aggressive manifestations, including lymphoma in SS with RA, require interdisciplinary help - hematologists.

## 2.7. Vasculitis

Rheumatoid vasculitis is a rare but most serious systemic complication of rheumatoid arthritis. It typically affects small and medium-size vessels. It occurs almost exclusively in patients with seropositive nodular RA who suffer from RA for at least 10 years and is associated with poor prognosis [116-118]. 40% of patients die within 5 years as well as significant mortality due to both organ damage from vasculitis and consequences of the treatment [119-121]. Although diagnostic criteria for systemic rheumatoid vasculitis were originally described in 1984 by Scott et al. [122], no validated definition of vasculitis exist. Recent studies suggest that rheumatoid factor, anti-cyclic citrullinated polypeptide (CCP) positivity, male gender, tobacco use, rheumatoid nodules, and older onset or long disease duration confer added risk of vasculitis [116]. Patients with the Felty's syndrome are also prone to vasculitis [121].

There appears to be a genetic predisposition toward developing rheumatoid vasculitis. RA studies focused mainly on the third hypervariable region of HLA-DRB1 called the shared epitope. Recent studies suggest a relationship between rheumatoid vasculitis and three specific genotypes of the HLA-DRB1 shared epitope: \*0401/\*0401, \*0401/\*0404, and \*0101/\*0401 [118]. Research performed by the Mayo Clinic described a new correlation of HLA-C3 with rheumatoid vasculitis [123]. Strong correlation of smoking with the development of rheumatoid vasculitis was also discovered [123]. Other studies have also supported this relation, not only in rheumatoid vasculitis but also in other extra-articular manifestations [124]. Higher levels of anti-cyclic citrullinated polypeptide (CCP) antibodies levels were observed in patients with RA, who have systemic vasculitis [125]. The presence of anti-CCP antibodies in patients with RA is linked to a progressive joint damage and severe extra-articular manifestations [121, 125]. During the studies of evaluating anti-CCP and RA vasculitis, antibodies were detected in 93% of patients with systemic RA vasculitis and only in 7% of patients with

primary systemic small vessel vasculitis [121, 125]. However many patients with RA who have circulating or tissue-deposited immune complexes and high levels of autoantibodies do not develop vasculitis [124]. Systemic inflammation accompanying the development of RA promotes early and aggressive atherosclerotic vascular disease which may present similar to vasculitis manifestations. In such case, histopathologic confirmation of vasculitis is required [124]. Characteristic histopathology confirmation of vasculitis is generally necessary for a diagnosis of rheumatoid vasculitis. Other clinical and laboratory features are often supportive and may be used to assist a follow-up [124].

Pathologic features of rheumatoid vasculitis include mononuclear cells or neutrophilic infiltration of the vessel wall of small and medium vessels. Features of vessel wall destruction are often found, including necrosis, leukocytoclasia, and disruption of the internal and external elastic lamina. An important observation is that inflammation of more than three cell layers of the vessel is a significant feature to distinguish rheumatoid vasculitis from RA without vasculitis [124,126]. RA vasculitis may involve a number of body organs. Manifestations differ depending on involved part of the body. The most common sites of involvement are the skin and peripheral nerves. Cutaneous manifestations of rheumatoid vasculitis include palpable purpura, focal digital lesions, nodules, ulcers, digital necrosis and pyoderma. Peripheral nervous system involvement may be represented by distal sensory or motor neuropathy, mononeuritis multiplex. Central nervous system involvement may result in transient ischemic attack, stroke, or seizure. Vasculitis development in the eye manifests in corneal ulceration and scleromalacia. Pulmonary involvement includes fibrosing alveolitis and alveolar hemorrhage. Vasculitis in major organs is much less common but can lead to significant morbidity and mortality, including myocardial infarction, bowel ischemia, and renal failure [124].

High incidence of cardiovascular-related deaths is observed in patients with RA. Dawson et al. noted that 31 % of the RA patients had an estimated pulmonary artery systolic pressure of 30 mmHg or more, and 21% of all the RA patients had pulmonary hypertension [127]. Severe pulmonary hypertension in patients with RA is not common and usually is associated with other collagen-vascular diseases such as progressive systemic sclerosis, syndrome of calcinosis, Raynaud's phenomenon, esophageal dysfunction, sclerodactyly and telangiectasia [128]. Pulmonary hypertension might be considered as primary or secondary. Primary pulmonary hypertension is often clinically silent until well advanced. It has a very poor prognosis and a median survival of only 2–3 years [129]. Secondary pulmonary hypertension progresses slower than the primary form. Treatment of pulmonary hypertension initially needs to be directed at the underlying cause. In RA, the pulmonary hypertension is usually a result of RA-associated lung disease and implies a poor prognosis.

A number of structural abnormalities have been reported in RA patients population. Aortic root enlargement, pericardial effusion, mitral valve abnormalities and impaired left ventricular function are more common in patients with RA than in control groups [127]. It has been noted that RA patients have an increased number of abnormalities related to the function of the left ventricle [130]. Impairment of left ventricular function may cause elevation of pressure on the left atrium which results in raises of the pulmonary artery pressure. Mild to

moderate primary pulmonary hypertension is a common case in the RA population. Dawson et al. identified that 31% of hospital RA patients have pulmonary hypertension on echocardiography. In these patients no significant symptoms, signs, ECG or structural echocardiographic changes were apparent, probably because of early stage of disease [127]. Shortness of breath as a result of cardiorespiratory disease in RA may appear because of constraints arising from RA. It was suggested that number of deaths that have been previously linked to ischaemic heart disease, may really have had been due to primary pulmonary hypertension [127].

A treatment of vasculitis depends on the degree of organ system involvement. Mild rheumatoid vasculitis involving the skin or peripheral nerves can be treated with prednisone (30-200mg/day) and methotrexate (10-25 mg/week) or azathioprine (50-150 mg/day). More serious organ system involvement may require treatment with higher-dose steroids and cyclophosphamide or biologic agents [124]. Management of patients with RA vasculitis should take into account the increased risk of comorbidities in particular from cardiovascular disease [121].

## 2.8. Pericarditis and myocarditis

Pericarditis is one of the most common extraskelatal manifestations in RA. It occurs in 30-50% of the patients [131]. The highest occurrence of the disease is observed in male patients with destructive and nodular RA [132]. It occurs seldom, require echocardiographic diagnostics which may show asymptomatic pericardial involvement. Symptoms can also include chest pains and pericardial effusion. Prognosis of RA patients with pericarditis depends on age, cardiac status. The prognosis is best when diagnosed in the first year [133]. Majority of patients develop pericarditis after arthritis begins, however pericarditis may also manifest before diagnosis of RA. Early diagnosis of RA is then relevant, and effective treatment improves the outcome of patients with RA [134]. Treatment with non-steroidal anti-inflammatory drugs, corticosteroids and/or other immunosuppressive drugs seems appropriate in the majority of patients with a definite diagnosis of RA-associated pericarditis, and in severe cases, pericardiectomy is required [135].

Patients with RA have a two to five times increased risk of developing severe and premature cardiovascular disease [136]. Relationship between cardiovascular risk and inflammation has been suggested. Endothelial dysfunction, reduced arterial elasticity and compressibility and increased atherosclerotic burden observed in RA support this theory [137-139]. Diffused necrotizing or granulomatous myocarditis may be a cause of cardiomyopathy. Postmortem histological studies showed cardiomyopathy in 3-30% of RA patients [131]. Pathogenesis includes myocyte injury, local and systemic cytokine-mediated immune responses, cell activation with cellular infiltration, oedema and necrosis [130]. It was hypothesized that elevated proinflammatory cytokines such as TNF- $\alpha$ , IL-1, IL-6 observed in RA may be associated with concomitant myocardial tissue injury [141]. These mechanisms occur to involve simultaneous activation of collagenolytic enzymes, MMPs [142]. Increased T2-ER observed in RA patients reflects ongoing inflammatory injury and persistence of tissue oedema in RA myocardium [141].

### 3. Case reports

These cases are included to illustrate the complexity, variety of course, complications and most common diagnostical problems with the rheumatoid arthritis.

#### 3.1. Case nr. 1

A 26 years old female with 14 years history of seropositive rheumatoid arthritis. She has very aggressive course of disease. While diagnosed rheumatoid arthritis she had elevated rheumatoid factor – 1030 IU/ml, highly positive level of anti-citrullinated protein/peptide antibodies (AC-PA) – 1137 U/ml, elevated level of inflammations factors - CRP, ESR. Furthermore she had objective factors of inflammations in the joints - overgrowth of synovium and infiltrations in joints cavity detected in ultrasound. The aggressive course of the disease correlates with progress in radiological changes in the joints. Radiogram of the hands shows Fourth Degree in Larsen Scale - it means that in the joints space there are severe erosions, with no joint space left and the original bone outlines are partly presented [143]. Radiograms of the legs show Second Degree in Larsen Scale - it means that in the joints space there are only one or several small erosions and diameter of the joints space is more than 1mm [143]. Therefore the patient required many surgical procedures. She underwent linear osteotomy of metatarsal bones of right foot in 2007 and had stabilizations of the left and right wrist with reconstruction of extensor palmaris of the second and third finger in the left hand in 2007. Then she received endoprosthesis of MCP II-III bones of the right hand in 2010. .

Physical examination showed symetric polyarthritis involving arms, wrists, metacarpophalangeal joints, proximal interphalangeal joints, knees, ankles and feet, 18- tender joints, 12- swollen joints, morning stiffness >120min, Disease Activity Score 28 (DAS28)- 6,67

She was treated with a variety of disease modifying antirheumatic drugs (DMARD's) over the years –sulfasalazine - in 2003 - 2007, chloroquine – in 2003-2007, cyclosporine – in 02.2009-04.2009 - with not good clinical response. After that she was treated with methotrexate. At first she was taking 7,5 mg i.m/week between 13.06.2007 - 18.09.2007. She showed intolerance to the drug – leucopenia. Next trial with methotrexate was in 17.03.2008 – 16.09.2008. She was treated with the dose of 10 mg -15 per os. She presented intolerance to the drug again- high level of liver enzymes, nausea. Methotrexate therapy was discontinued definitely. Next she received leflunomide – 20 mg/day from 04.02.2009 to 06.04.2009, also showing bad tolerance - leucopenia, high level of liver enzymes. After the DMARD's therapy failed, she was treated with anti TNF- $\alpha$  - etanercept 50mg sc/week for almost 2 years. In the end the patient did not show enough clinical response (difference between courses DAS28 < 1,2) and the therapy was canceled. Then she took tocilizumab - 480mg i.v./month – monotherapy - 6 courses, good response. Her Disease Activity Score 28 (DAS28) went near remission 2,98.

This case shows the patient in early age with very aggressive course of disease. She had high level of rheumatoid factor and anti-CCP antibody. She developed high level of radiological changes in joints and required surgical procedures. Her other risk factor of aggressive rheumatoid arthritis is poor response to disease modifying antirheumatic drugs and anti TNF- $\alpha$ .

This is a classical example of patient who has statistically high level of risk factor to develop destructive course of rheumatoid arthritis.

The most important thing in diagnostic process is to recognize a patient with high risk of aggressive course of the disease. Next the patient should receive appropriate treatment that includes combined therapy of at least two different DMARD's (disease modifying antirheumatic drugs ) and in case of ineffectiveness of this therapy – also biologic agents. In case of seropositive RA with methotrexate intolerance patient should receive anti-TNF- $\alpha$  therapy in monotherapy (etanercept or adalimumab). If this therapy is not successful patient should be receiving inhibitor IL-6 – tocilizumab or fusion protein bind CTLA-4 - abatacept. This treatment can slow down or even stop the progression of the disease [144].



**Figure 1.** Case nr.1. A 26-year old woman with 14 years of rheumatoid arthritis. She underwent linear osteotomy of metatarsal bones of right foot in 2007 and had stabilizations of the left and right wrist with reconstruction of extensor palmaris of the second and third finger in the left hand in 2007. Then she received endoprosthesis of MCP II-III bones of the right hand in 2010.

Radiological changes are the visual outcome of the progressive rheumatoid arthritis. Thus, developed erosions in the joints in early stage of the disease prove joints destruction and probability of functional disability. There are predictive factors of long-term radiographic outcomes in early rheumatoid arthritis. N. Courvoisier performed a long-term study of 10 years to investigate predictive factors of radiographic outcome in RA and found the best independent predictive factor of the 10-year radiographic score to be baseline erosion score [145]. According to N. Courvoisier high level of erythrocyte sedimentation rate (ESR), presence and level of IgA rheumatoid factor, presence of an anti-citrullinated protein antibody (ACPA), serum level of matrix metalloproteinase-3 and radiographic score at baseline are the most important factors to predict which patients will develop severe form of rheumatoid arthritis. Interesting conclusion from this research work was that several demographic and clinical parameters, such as sex, age and number of tender or swollen joints, have not been shown to be independent prognostic factors [145].

### 3.2. Case nr. 2

A 48-year old female diagnosed with seropositive rheumatoid arthritis in 2004. Since 2004 the patient was treated with prednisolone, at the highest dose of 15mg/day. She has also received nonsteroidal anti-inflammatory drugs (NSAIDs) - paracetamol, ibuprofen, naproxen, diclofenac, recently ketoprofen. Since 2005 she has not taken any disease modifying anti-rheumatic drugs (DMARD's), although methotrexate and sulfasalazine were prescribed. The patient on her own decided to stop the treatment and did not cooperate with physicians.

In the spring of 2012 patient was admitted to the Department of Systemic Connective Tissue Diseases in Institute of Rheumatology with big flare-ups. Assessed Disease Activity Score 28 (DAS 28) was 7.22 (22 painful joints, 13 swollen joints, VAS-80, ESR-34mm/h). She has elevated rheumatoid factor - 681IU/ml, highly positive level of anti-citrullinated protein/peptide antibodies (ACPA) - 263,5U/ml. Physical examination revealed numerous rheumatoid nodules, with diameter range from 2 to 3 cm. The nodules were located on the extensor parts of the proximal interphalangeal and metacarpophalangeal joints and around wrists and ankles and elbows. The radiographs showed advanced changes from rheumatoid arthritis, ankylosis, joints subluxations, the highest degree of radiological V, according to Larsen - it means mutilating changes, where the original bony outlines have been destroyed [143].

In therapy the patient received the reference dose of methotrexate (25mg per week), the dose of glucocorticosteroids was reduced to 7,5mg/ day, and the dose of ketoprofen was reduced to 100mg per day. Patient was admitted to the Department one month after the start of the therapy. Disease Activity Score 28 went down to 3,3 (2 painful joints, 1 swollen joint, VAS- 55.) Inflammatory parameters were reduced ( ESR-8mm/h, CRP- 3 mg/dl).

The purpose of the presentation of this case is to show a patient with aggressive natural course of disease, advanced articular changes and extra-articular complications - rheumatoid nodules. Rheumatoid nodules are benign structures, that relate to positive rheumatoid factor in 90%. Although there is no correlation between nodules, rheumatoid arthritis progression and severity of this disease, patients with rheumatoid nodules are recommended to take more aggressive treatment. Rheumatoid nodules are a cosmetic issue and do not require treatment, however complications can occur. There is high probability of infection, ulceration or even gangrene. Sometimes the internal nodules cause fistula. In this case there is a need for the surgical procedure. When nodules are painful, limit the motion or damage the underlying structures, the injection of corticosteroids can reduce these symptoms. Conventional treatment (DMARD's) usually reduce or even completely resolve rheumatoid nodules. There are however published cases of accelerated rheumatoid nodules, that respond differently to the conventional treatment. In 1986 Kremer and Lee described the occurrence of such nodules during a study of a long-term methotrexate therapy [146]. Three patients had an increasing number of nodules during a therapy of methotrexate. Since then there has been a lot more descriptions of complications of methotrexate therapy. Usually patients complain of small, painful nodules on the hands - metacarpophalangeal and proximal interphalangeal joints, feet and ears. These observations were confirmed by Ahmed and coworkers. They arranged double blind study with methotrexate and azathioprine with patient with rheumatoid arthritis. Study showed an 8% incidence of methotrexate-induced accelerat-

ed rheumatoid nodules with arthritis improved and none of azathioprine [147]. Combined therapy- methotrexate and one of the following drugs: hydroxychloroquine [148], D-penicillamine [149], colchicine [150] or sulfasalazine [151] reduce probability of incidence of accelerated rheumatoid nodules. There are also case reports of another drug which have been implicated in occurrence of accelerated rheumatoid nodules. Anti-TNF- $\alpha$  therapy with etanercept can cause appearance of rheumatoid nodules.



**Figure 2.** Case nr.2. A 48-year old female diagnosed with seropositive rheumatoid arthritis. She has numerous rheumatoid nodules.

The case report described above shows a patient with numerous rheumatoid nodules. This case is not related to the complications of methotrexate therapy, this is a typical case, where methotrexate decreased the size of nodules. However, there is an example of patient with very advanced clinical stage of rheumatoid arthritis (ankylosis in the hands during 7 years natural course of the RA). In the era of disease modifying antirheumatic drugs and biological treatment such case should never have happened. Patients who are quickly diagnosed with RA, should receive appropriate treatment within three months from the diagnosis. First step is DMARD's therapy. After three months of combined therapy (two different DMARD's including methotrexate 25mg/week [152]), patients require anti-TNF- $\alpha$  therapy combined with methotrexate. If this treatment fails, patients with seropositive RA should undergo an anti CD20 therapy – rituximab [153]. If the patients are seronegative RA, they should receive another biological agent (inhibitor IL-6, or anti IL-1 or fusion protein bind CTLA-4) [144]. Only this way patients with RA are able to significantly reduce the chance of disease progression.

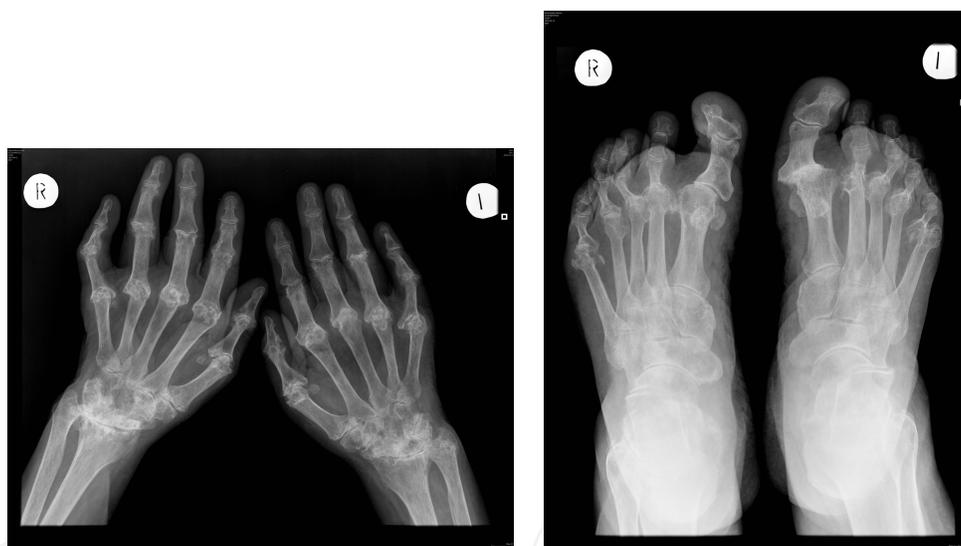
### 3.3. Case nr. 3

A 68 year old patient, diagnosed with seropositive rheumatoid arthritis in 1978. In 2007 the patient was diagnosed with kidney failure based on the functional parameters of kidney: (creatinine 2.1 mg/dl, urea 150mg/dl, GFR-60) - renal insufficiency, (proteinuria over 3.5 grams/day, hypoalbuminemia, edema of lower limbs) - nephritic syndrome. Biopsy obtained from adipose tissue showed amyloidosis associated with RA. The patient has been hospitalized at the Institute of Rheumatology since 2008. She was admitted from Nefrology Department with severe microcytic anemia (Hb-7,6 g/dl, MCV- 83fL) after blood transfusion. She received 4 units of blood and she was qualified to erythropoietin treatment. She has also big exacerbation of rheumatoid inflammations (ESR- 107mm/h, CRP-86mg/l), Diseases Activity Score 28 (DAS28)- 6,69 ( 9-swollen joints, 9-painful joints, VAS-64). The patient was diagnosed with secondary Sjogren's syndrome based on dry mouth and eyes, positive Schirmer test - keratoconjunctivitis sicca and histopathological examination - focus score of 2. The radiographs show advanced changes of rheumatoid arthritis with presence of erosions and joint subluxations - the highest degree of radiological V, according to Larsen- it means mutilating changes, where the original bony outlines have been destroyed [143]. She was treated with small doses of glucocorticosteroids and cyclophosphamid. The patient tolerated well the first 2 grams of cyclophosphamid treatment. Further therapy went with complications. After the patient fell down on the left shin, she has had abscess. Staphylococcus aureus grew in bacteriological sowing. Patient received antibioticotherapy, cytostatic treatment was stopped. After one month of antibiotic therapy, the Staphylococcus was still present in the sowing from endoprosthetic knee. She took antibiotics for over six months. In 2010 the patient received cytostatic treatment one more time. There was no bacteria present anymore. After administering the second gram of cyclofosfamid there was an increase of renal insufficiency, therefore the cyclostatic treatment was terminated. Over a 34-year period of time, the patient received various disease modifying antirheumatic drugs (DMARD's) - sulfasalazine, hydroxychloroquine, cyclosporine, gold salts - with no therapeutic effect. Patient does not tolerate methotrexate, azathioprine and cyclophosphamid. Currently patient is treated with anti-TNF- $\alpha$  monotherapy with good tolerance, low inflammatory parameters and stabilization of kidney functions.

The description of this case is to show an aggressive course of disease with multiple exacerbations. The patient was treated with different drugs, which were ineffective or had side effects and in the end showed multiple organ damage. The most dangerous is renal failure caused by amyloidosis. In secondary amyloidosis AA renal involvement is observed in approximately 90% of all cases. Serum amyloid A (SSA) is responsible for amyloid deposits in involved organ. Concentration of amyloid A is proportional to inflammations process. Amyloidosis is diagnosed after about 17 years (4-40) of active rheumatoid arthritis [154]. Amyloid deposits concentrate in the renal capsule, particularly in mezangium, in the Bowman's capsule, but also in the renal pelvis, perynchema and in renal vessels. 95% of patients with secondary amyloidosis have proteinuria [155], nephritic syndrome or a different kind of kidney failure (hematuria, defect of renal pelvis or urinal infections). Main aim of the therapy in systemic amyloidosis is reducing and eliminating existing protein production or prohibiting further deposition of amyloid fibrils in organs.

The easiest way to reduce serum amyloid A is to reduce inflammations process by reducing CRP level by use DMARD's therapy [156] or anti -TNF- $\alpha$  therapy [157]. TNF- $\alpha$  inhibitor achieved therapeutic success by reducing level of serum IL-6 [158,159]. Low level of serum IL-6 stops the synthesis of acute-phase proteins, systemic inflammation is suppressed, and SAA levels are lowered by decreasing polymorphism SAA1 gene. This suppresses hepatocytes leading to reduction of amyloid deposits. New alternative is inhibitor IL-6- tocilizumab, a drug that directly inhibits polymorphism SAA1 gene [160,161].

Another way to stop amyloidosis is to reduce amyloidogenesis by stabilizing amyloid deposits in tissues. This aim can be achieved by interactions between amyloidogenic proteins and glycosaminoglycans promote fibril. There is a drug – eprodisate - which stops binding of SAA protein to precursor, next prohibiting polymerization of amyloid fibrils and deposition of the fibrils in tissues [162]. In 2007, Dember and coworkers published a multicenter, randomized, double blind, placebo-controlled trial to evaluate the efficacy and safety of eprodisate in patients with AA amyloidosis and kidney involvement. Eprodisate slow progression in the renal, stabilize renal functions and stop progression of amyloid deposits [95].



**Figure 3.** Case nr 3. A 68 year old patient, diagnosed with seropositive rheumatoid arthritis, secondary amyloidosis. Advanced changes in joints, the highest degree of radiological V, according to Larsen

The patient described above received the appropriate treatment. Rheumatoid arthritis and secondary amyloidosis required first classic treatment - DMARD's therapy (first drug in this case is cyclophosphamid) with glucocorticosteroids, next in case of this treatment's failure - anti-TNF- $\alpha$  therapy or inhibitors IL-6.

### 3.4. Case nr. 4

A 45 year old female was diagnosed with seropositive rheumatoid arthritis in 2000. She was treated with sulfasalazine, hydroxychloroquine and low dose of prednisolone.

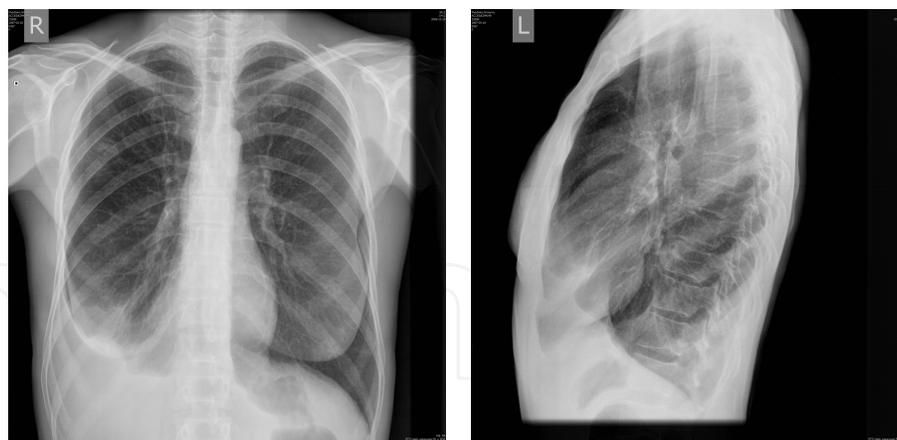
On the December of 2006 the patient was admitted to the Department of Pulmonology with dyspnea and chest pain. Pleuritis with pleural effusion and degraded mass in the right lung were revealed based on chest X-ray. Bronchoscopy with cytology was taken. The result excluded bacterial infections and tuberculosis (cultures, PCR). Patient did not consent to pleural puncture. Tuberculostatic treatment was induced without influence on described lung changes. After 6 months pleural puncture was performed aspirating 1100ml of effusion fluid. The fluid had 46% of lymphocyte, very low level of glucose and highly positive rheumatoid factor, suggesting inflammation associated with RA exacerbation. Further investigations excluded heart failure and lung cancer. CT scan showed pleural effusion and mass (1,8 centimeters) suggested rheumatoid nodule in the third segment of right lung. The biopsy confirmed the diagnosis.

Patient was admitted to the Department of Rheumatology. Physical examination showed exacerbation of RA: 13 swollen joints, 11 painful, VAS - 68, ESR - 15mm/h and DAS28 - 5.8. Laboratory test revealed positive rheumatoid factor. Radiograms showed third degree in Larsen Scale (marked erosions in the joint surfaces). Other connective tissue diseases were excluded. The patient received 40mg/ day of methylprednisolone and methotrexate. The treatment was ineffective. Although the patient felt better, there were decreased swollen and painful joints with the same amount of fluid effusion. The treatment was switched to sulfasalazine, hydroxychloroquine and methotrexate. It turned out that the patient does not tolerate methotrexate. On April of 2008 the patient was started on leflunomid treatment with good tolerance. The disease activity decreased to medium-low (DAS28 = 3.04). The inflammation in the lungs stabilized with a tendency to decrease in the amount of fluid in the pleural cavity.

This case shows that the image of RA can vary. A patient with rheumatoid arthritis requires an interdisciplinary care and multi-diagnosis. Therapies should be directed not only toward the treatment of arthritis, but also treatment of exacerbation of respiratory failure.

Pleural involvement is the most common manifestation of lung disease in rheumatoid arthritis. The prevalence is estimated to 5-20% patients with rheumatoid arthritis [61]. Other lung manifestations in rheumatoid arthritis are: rheumatoid nodules, interstitial lung diseases (heterogeneous group of disease depending of damage to the lung by inflammation or fibrosis), pulmonary hypertension, methotrexate induced lung diseases.

Traditional treatment of lung involvement in rheumatoid arthritis is corticosteroids. When there is pleural involvement, the treatment includes drainage of recurrent symptomatic effusion and oral corticosteroids, and treatment for the underlying rheumatoid arthritis. Next alternative treatment, especially for lung fibrosis, are cyclophosphamide [163], cyclosporine, azathioprine [163], and hydroxychloroquine [80]. Some case studies by Antoniou KM et al. suggest that infliximab may have an effect on interstitial lung diseases associated with rheumatoid arthritis. This study showed that infliximab can lead to stabilization or improvement of symptoms, lung function and lung image in X-rays [164].



**Figure 4.** Case nr 4. A 45 year old female was diagnosed with seropositive rheumatoid arthritis, and lung involvement. X-rays showed right pleural effusion and in upper-middle side of right lung there was 1.6 centimetres mass looked like rheumatoid nodule.

## 4. Conclusion

Rheumatoid arthritis' course may vary. The occurrence of extraskeletal manifestations requires different diagnostic procedures and treatment. Many of extraskeletal manifestations are associated with more active or aggressive course of RA. Currently there are no predictors for extraskeletal manifestations which may suggest their presence in course of disease, although they are associated with risk factors like smoking, age, sex, level of inflammatory mediators, presence of rheumatoid factor, antinuclear antibodies and genetic factors. Extraskeletal features of RA are common and generally linked with aggressive course of disease. They need to be recognized early and treated in proper way.

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