ORIGINAL PAPER

RJME
Romanian Journal of Morphology & Embryology
http://www.rjme.ro/

Rheumatoid nodules and quality of life in rheumatoid arthritis females – complex assessment

MAGDALENA-RODICA TRĂISTARU[1)], DIANA KAMAL[2)], DIANA-MARIA TRAŞCĂ[3)], MARIA-CAMELIA FOARFĂ[4)], CORINA-LAVINIA GRUIA[4)], OTILIA-CONSTANTINA ROGOVEANU[1)]

[1)]*Department of Physical Medicine and Rehabilitation, University of Medicine and Pharmacy of Craiova, Romania*
[2)]*Research Center for Microscopic Morphology and Immunology, University of Medicine and Pharmacy of Craiova, Romania*
[3)]*2nd Department of Medical Specialties, University of Medicine and Pharmacy of Craiova, Romania*
[4)]*Department of Pathology, Emergency County Hospital, Craiova, Romania*

Abstract

Rheumatoid arthritis (RA) represents the most commonly diagnosed arthropathy that affect many tissue types and organs, characterized by a clinical, functional and therapeutic pathogenic complexity and it affects especially diarthroidal joints. Rheumatoid nodules (RNs) are one of the most frequent extra-articular manifestations of RA, and usually reflect an advanced stage of the disease and a poor prognosis. The complexity of histological, clinical and functional aspects in RA has a real impact on the quality of life in all patients diagnosed with this disorder. Our prospective study presents the RNs involvement in the rehabilitation program performed in order to enhance the quality of life in the 25 RA female patients. We made a complex assessment and realized a correlation between pain, disability and histological aspect of RN, before and after the rehabilitation program. Also, we evaluated the clinical and functional effectiveness of a complex rehabilitation program and changes in impairment and activity limitation in women with RA and RNs. The immunohistological complexity of RNs reflects the intensity of the inflammatory-immune process and completes the assessment of RA patients with RNs. It allows for medical assistance quantification, even for patients that have a poor evolution prognosis.

Keywords: rheumatoid arthritis, nodule, quality of life.

Introduction

Rheumatoid arthritis (RA) – a serious, systemic auto-immune disease characterized by a chronic inflammatory process [1] – represents the most commonly diagnosed arthropathy that may affect many tissue types and organs, characterized by a clinical-functional and therapeutic pathogenic complexity, which affects especially diarthroidal joints (wrists, fingers, feet, knees or ankles) [2, 3]. The hallmark feature of RA is persistent symmetric polyarthritis (synovitis) that affects the hands and feet, although any joint lined by a synovial membrane may be involved.

RA affects approximately 1% of the adult population in general, but this percentage increases with age. After age 55, the prevalence rises to 5% in females and 2% in males. With an incidence rate of 0.03% and a point prevalence of 0.5 to 1%, RA affects between 5 and 50 per 100 000 new people each year in the developed world [2, 4]. In our country, the annual incidence is 0.5 new cases per 1000 in females and 0.2 new cases per 1000 in males [4]. The severity of RA may fluctuate over time, but chronic RA most commonly results in the progressive development of various degrees of joint destruction, deformity, and a significant decline in functional status. The natural course of this chronic disease is almost invariably one of persistent symptoms and a progressive deterioration of joint structures leading to deformations and disability [5]. RA – a major cause of morbidity, mortality and health care utilization [3] – has a major impact on well-being and quality of life [6].

Patients affected by RA, experience a disabling and painful condition, which can lead to substantial functional limitation related to both complex joint impairment and skeletal muscle dysfunction, if not adequately treated. Patients may report difficulty-performing activities of daily living (ADLs), such as dressing, standing, walking, personal hygiene, or use of hands. In addition to articular deterioration, constitutional symptoms (fatigue, malaise, morning stiffness, weight loss, and low-grade fever) may be present.

Rheumatoid nodules (RNs) are characterized by sub-cutaneous nodular lesions at pressure areas, such as finger joints and the extensor area of the forearm – are one of the most frequent extra-articular manifestations of RA, seen in approximately 20% to 40% of patients, and generally occur in patients with a severe and seropositive form of the disease [rheumatoid factor (RF) is almost invariably present in patients with rheumatoid nodules; the absence of RF suggests other diagnoses]; usually, reflect high levels of disease activity and poor prognosis [7, 8]. They occur in fewer than 10% of patients during the first year of the disease. These lesions are described primarily in the subcutaneous tissue, either around pressure points, such as the elbow and Achilles tendon or at the site of chronic trauma [8]. RNs are most commonly found on extensor surfaces or areas of frequent mechanical irritation: proximal ulna, on the olecranon process (where they must be differentiated from a bursitis olecrani with enlargement of the synovial layer), the back of the head and ears, the back of the heels, and the ischial tuberosities [9]. Nodules may also form in the subcutaneous tissues of the fingers,

in toes and heel pads, in tendons (especially extensor tendons of the hand, at the level of the metacarpophalangeal or the proximal interphalangeal joint) and in viscera [4]. The histological features of RN are represented by fibrosis with granulomatous areas of palisading tissue, macrophages around a central necrotic area; occasional multinucleated giant cells are seen [9].

The complexity of histological, clinical and functional aspects in RA has a real impact on the quality of life in all patients diagnosed with this disorder. This paper will discuss in detail, the rheumatoid nodule involvement in the rehabilitation program performed to enhance the quality of life in RA female patients. We evaluated the clinical and functional effectiveness of a complex rehabilitation program (performed for two weeks) on changes in impairment and activity limitation in women with RA and RN over a six-week period.

Patients and Methods

Between 2012–2014, we performed a prospective study: 25 Caucasians females' patients, over the age of 50 (average age 54.12 years, between 49 and 62 years), previously diagnosed with seropositive RA according to the *American College of Rheumatology* (ACR) criteria, and underwent complete examination (clinical, functional and imagistic evaluation) in the Department of Physical Medicine and Rehabilitation, "Filantropia" Municipal Hospital, Craiova, Romania.

We did not use the new classification criteria for RA established by the *American College of Rheumatology* and *European League Against Rheumatism* in 2010 [10], because our patients were diagnosed with RA before 2010 and had a moderate duration of disease. No patient was treated with biological therapy; they continued to take their previously prescribed medication (Methotrexate or Leflunomide) and non-steroidal anti-inflammatory drugs (NSAIDs) or corticosteroids for controlling pain and inflammation, for short-term management. Only eight patients received surgery for the RN localized on the olecranon process. These eight patients were available for the histological assessment.

We considered that a multifactorial approach was necessary for utilizing medication, diets and rehabilitation program for our patients.

Studied patients were completely assessed before and after completing the rehabilitation program. Patients were excluded from the study if they had significant comorbidities (malignancy, sever cardiovascular or pulmonary disease or psychiatric disorder).

In the clinical assessment, we made a general clinic estimation, the subjective and physical examination of all segments of skeletal status and carefully examination for the presence of RN, and mentioned the number (single or multiple), location and dimensions.

After the clinical exam, we made a functional evaluation and noted the functional capacity grade (class) for our patients, in accordance with Steinbrocker's classification of functional capacity (STB) and ACR revised global functional class (a quick and simple method for classifying functional capacity, extensively used by rheumatologists over the past 40 years) [11].

Laboratory studies included: baseline complete blood count and renal and hepatic function tests (creatinine level, hepatic enzyme levels, urinalysis), total cholesterol and triglyceride (for pattern of dyslipidemia), rheumatoid factor, anti-citrullinated protein antibody, C-reactive protein levels (CRP, g/mL) and erythrocyte sedimentation rate (ESR, mm/hr – first hour) to establish the level of RA activity and to follow disease activity and response to treatment. We could not determine the specific human leukocyte antigen (HLA-DR4, HLA-DR1).

All studied females had conventional posterior–anterior radiographs of the hands and wrists (to assess the bone erosions).

Parameters measured before and after six weeks after rehabilitation program were: pain (VAS – visual analogue scale, VAS 0–10; 0 indicated a painless status and 10 a most severe pain); we considered the global patient pain status; disease activity was evaluated by the Disease Activity Score (DAS28); we used the DAS28 (ESR) [12]; ultrasound aspect of RN and other ultrasound finding of diarthroidal joints; the ultrasound examination was performed with the ESAOTE Ultrasound System, 7.5 MHz linear probe; histological exam of RN; we performed two histological exams: histopathological (HP) – the biological material was processed using the standard paraffin embedding technique, with the following steps: 10% buffered formalin fixing, washing with water or 80% alcohol, dehydration – in a graded alcohol, to clarify – graded benzene, toluene, xylene and paraffin. Staining was done with the usual Hematoxylin–Eosin (HE). Immunohistochemistry (IHC) – LSAB method was used (HRP) (LSAB – Labeled Streptavidin Biotin, HRP – Horseradish peroxidase) antibodies: CD10, CD20, CD45RO, CD68, S100, vimentin (Table 1).

Table 1 – ***Antibodies used in our study***

Antibody	Source	Clone	Dilution	Antigen retrieval
CD10	LEICA	56C6	1:100	Five cycles, citrate buffer
CD20	DAKO	L26	1:100	Three cycles, citrate buffer
S100	DAKO	Polyclonal	1:500	–
Vimentin	THERMO	V9	1:100	Five cycles, citrate buffer
CD68	DAKO	PG-M1	1:100	Seven cycles, citrate buffer
CD45RO	DAKO	UCHL1	1:200	Seven cycles, citrate buffer

HAQ (*Stanford Health Assessment Questionnaire Disability Index*) questionnaire for quantify the functional status expressed through important activities of daily living, measurement of functional ability and patient quality of life [13]. Eight categories, reviewing a total of 20 specific functions were used to evaluate patient difficulty with activities of daily living over the past week. Increasing scores indicate worse functioning with 0 indicating no functional impairment and 3 indicating complete impairment. In Table 2, we mentioned the demographic and other clinical characteristics of subjects. All RA studied females were treated by means on physical therapy for a period of 14 days (10 sessions, one session daily, five days a week).

Table 2 – ***Demographic, clinical and paraclinical parameters of patients***

Parameters	PreRP			PostRP		
Age [years]	54.12±2.635 (49–62)					
Own place	20 p. – urban place, 5 p. – village place					
RN	5 p. – one place (RN1), 12 p. – two places (RN2), 8 p. – three places (RN3)					
ACR class	11 p. – 2 class ACR (ACR2), 14 p. – 3 class ACR (ACR3)					
ESR	44.32±4.679 (34–55)			37.36±5.886 (23–51)		
VAS	5.08±0.812 (4–7)			3.08±0.572 (2–4)		
	RN1	***RN2***	***RN3***	***RN1***	***RN2***	***RN3***
	4.20±0.447	5.08±0.515	5.63±0.916	3.40±0.548	2.92±0.669	3.13±0.354
	ACR2		***ACR3***	***ACR2***		***ACR3***
	5.00±0.894		5.14±0.770	3.09±0.701		3.07±0.475
DAS28	4.384±0.846 (2.1–5.1)			4.116±0.840 (2.0–5.0)		
	RN1	***RN2***	***RN3***	***RN1***	***RN2***	***RN3***
	4.50±0.961	4.52±0.652	4.10±1.06	4.16±1.004	4.24±0.644	3.90±1.054
	ACR2		***ACR3***	***ACR2***		***ACR3***
	3.83±0.895		4.81±0.503	3.56±0.852		4.55±0.533
HAQ	13.32±1.842 (10–16)			10.68±1.973 (8–14)		
	RN1	***RN2***	***RN3***	***RN1***	***RN2***	***RN3***
	11.80±1.095	13.58±1.929	13.87±1.727	9.40±0.894	11.08±2.021	10.88±2.232
	ACR2		***ACR3***	***ACR2***		***ACR3***
	13.45±1.864		13.21±1.888	11.09±2.023		10.63±1.946

RP: Rehabilitation program; p.: Patient; RN: Rheumatoid nodule; ACR: American College of Rheumatology; ESR: Erythrocyte sedimentation rate; VAS: Visual Analogue Scale; DAS28: Disease Activity Score; HAQ: Stanford Health Assessment Questionnaire Disability Index.

After the multidisciplinary examination, a complete program (educational, medication, physical, kinetic) was applied and its components were: hygiene, diet and life regime, including educating the patient about the disease and the consequences of joint damage and disturbing hand function; all subjects received a joint protection writing rules – the principles of joint protection, energy conservation aspects, postural advice and fundamental adaptations for household activities; physical treatment [transcutaneous electrical nerve stimulation (TENS) in painful joints, and iontophoresis to both hands]; massage (sedative and the Cyriax massage); the entire upper limbs were massaged before and after kinetic session; assistive devices (canes, railings, adapters for making utensils easier to hold); physical therapy (exercises were balanced with rest, in painless and functional joint positions; the daily kinetic program was focused on stretching, strengthening and aerobic conditioning while conserving energy). All the rehabilitation team's efforts were focused to alleviate pain and to decrease the inflammation, to control the joint damage and the loss of limb function, to maintain function for activities of daily living and work, and maximize quality of life. Written informed consent was obtained from each patient.

SPSS 9.0 software package was used to perform the analysis and statistical significance was recognized at the level of $p<0.05$. Comparisons between variables were performed by analysis of variance. The associations between patient characteristics and the measured values were estimated by calculating Pearson's correlation coefficient. The differences between the associated regression coefficients of similar outcome measures were tested using regression analysis.

Results

Clinical and biological assessment

The mean age of patients was 54.12 years (standard deviation – SD 2.63, range 49 and 62 years). Average disease duration was 8.88 years (SD 2.18, range 6 and 14 years).

Twenty studied females lived in urban areas while five of them lived in a rural community (see Table 2).

After clinical examination, we established that five patients had only one location of RN (elbow or hand finger), 12 patients had two locations of RN (elbow and hand fingers) and eight patients had three locations of RN (elbow, hand fingers and foot). The last two groups were included in the third functional class; in the second functional class, 11 patients were included.

The values of the disease evolution parameters allowed an optimal rehabilitation program. In Table 2 are shown the laboratory findings (average values). Laboratory tests showed moderate inflammation. Tests for RF were positive and 60% of our patients had anti-citrullinated protein antibody.

After the complete examination, we confirmed that no patients had any form of cancer. We made clinical and laboratory exams with maximum attention because chronic inflammation is a major risk factor for the development of neoplasm in RA patients [14].

We obtained the following results for the measured parameters: VAS pain scale score had a favorable evolution, the improvement percent is important for patients with three areas of RN (the improvement percent of the painful status was 20% for category RN1, RN2 and 42–44% for RN3); in terms of functional class, the percent of pain reduction parameter was approximately equal (38% for patients in class ACR2 and 40% for class ACR3). We consider that the evolutionary pain parameter justifies the determinism complexity for the clinical-functional status in RA; tolerance for the electrotherapy program in combination with kinetic measures of limb orthopedic hygiene is an effective argument for medical rehabilitation in patients with chronic forms of RA. VAS-pain scale showed the highest correlation with RN ($r=0.61$), and the second highest correlation was with HAQ, after

rehabilitation program (r=-0.457, inverse correlation) (Pearson's correlation).

All patients had moderate (3.2 or more to 5.1 or less) disease activity (the median patient DAS28 was 4.384 with SD 0.846, range 2.1 and 5.1). We calculated DAS28 (ESR). Both measures DAS28 (ESR) and DAS (CRP) are useful for assessing disease activity in patients with rheumatoid arthritis; the validation profile was similar [12]. Although changing the parameter was favorable, there was a significant improvement (over 0.6), which allows us to assess the evolution towards disease remission. The fact that this parameter was not aggravated and no patient was situated in the severe form of the disease, confirms the benefit of the rehabilitation program, even in subjects with unfavorable prognosis of disease due to the presence of RN. DAS28 showed the only significant correlation with HAQ (r=0.54).

Functional assessment

The distribution of RA studied women by level of functional capacity on the ACR revised global function classification (Steinbroker's classification) is mentioned in Table 2. No patient was classified into functional class I. Eleven patients were able to perform usual self-care and vocational activities but limited in avocational activities (class II – ACR2) and other 14 patients were included in the third functional class (ACR3); had limited ability in performing usual self-care, vocational, and avocational activities; these patients had a long history of disease and three locations of RN (elbow, hand fingers and hallux).

Quality of life (QoL) for the studied patients had improved by 20%. This percentage was common for all included patients, regardless of functional class category (ACR2 or ACR3) number of locations or NO. The minimum percentage of improvement of 17% in patients with ACR2 class, value explained by the fact that these women showed a greater initial independence in carrying out daily activities and the rehabilitation program only allowed adjustments to these activities. Although patients with moderate forms of the condition were included in our study, severity of condition is not synonymous with level of QoL. Swelling of the elbow joints and wrists leads to severe pain and stiffness, especially in the morning. Chronic inflammation forced fingers to twist in an outward direction, and disturbance of the fine motor skills. The hand complex becomes disfigured and interferes with quality of life. This is the reason for the established value of HAQ.

When we took into consideration the linear regression for HAQ and the presence of RN, the value of R (correlation coefficient) was 0.920; R-squared (predictivity) was over 0.846, so over 80% of the cases studied follow the model of linear regression equations also confirmed by ANOVA. The frequencies graph is expressed in the curves form Figure 1a. When we took into consideration the linear regression for HAQ and the presence of RN and functional status (ACR), the value of R was 0.926; R-squared was over 0.861, so over 85% of the studied cases follow the model of linear regression equations also confirmed by ANOVA. The frequencies graph is expressed in the curves form Figure 1b.

Imagistic assessment

The complex hand-radiograph exams were in accordance with literature data [4]. The ultrasound exam of RN confirms the differential diagnosis of other periarticular joint tumors. It was helpful for visualizing soft tissue in the surrounding joint tissues. The ultrasound observed lesions that were characterized by a heterogeneous hypoechoic mass, well defined limits, with single contour sign, representing RN (Figure 2).

Histological assessment. Rheumatoid nodule exams

Nodules were located in the patient's elbows, the hand fingers and metacarpophalangeal joints and toes. They ranged in diameter from 0.5 cm on the hand (Figure 3a) to 4 cm on the left elbow (Figure 3b). The largest nodules, which were located in the elbow regions, were surgically removed. All RN were felt as cystic lesions, with firm immovable masses (the small RN) or soft mobile masses (the RN large than 2 cm, especially the ones located on the olecranon process of the elbow). Patients with multiple nodules mentioned that RN appeared and gradually increased in size. The patients complained of minimal pain and stiffness around the joints and nodules, but significant disabilities for activities of daily living. Elbow involvement was commonly accompanied by a flexion deformity, such as in contractures.

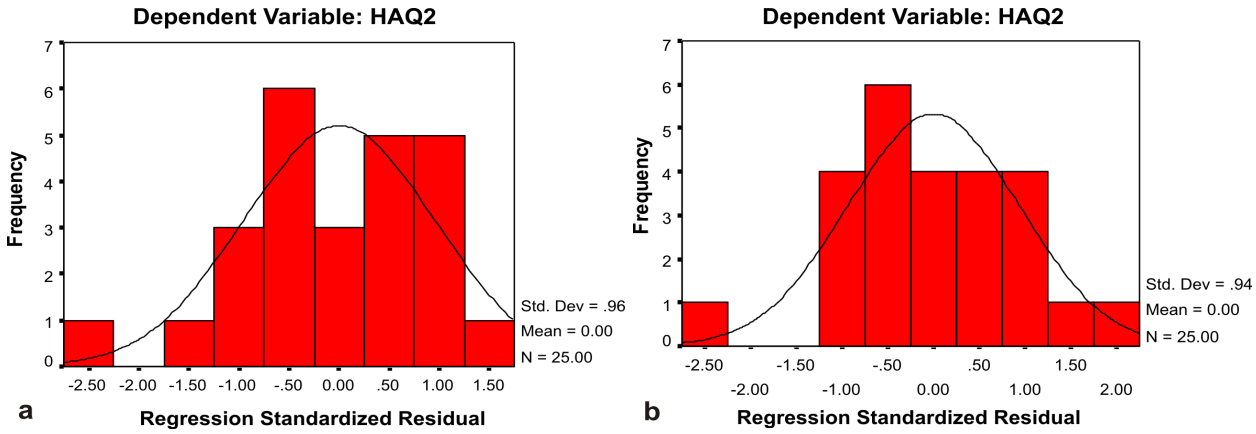

Figure 1 – ***(a) The frequencies graph corresponded to the linear regression for HAQ and the presence of RN; (b) The frequencies graph corresponded to the linear regression for HAQ and the presence of RN and functional status (ACR). HAQ: Stanford Health Assessment Questionnaire Disability Index; RN: Rheumatoid nodule; ACR: American College of Rheumatology.***

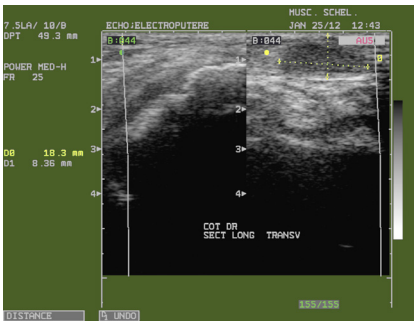

Figure 2 – ***Ultrasound image of a RN localized by the right olecrani.***

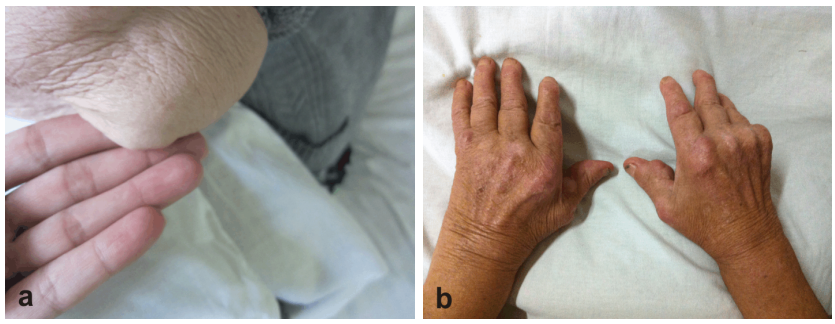

Figure 3 – ***(a) RN on the left elbow (4 cm diameter); (b) RN on the hand fingers (diameter ranged from 0.5 cm to 1 cm).***

The presence of RNs, an extra-articular manifestation, is associated in our patients with a moderate or reduced inflammatory state of the joints, in accordance with the literature, for RA patients treated with Methotrexate: the patients whose joint symptoms were improving after the administration of this drug often developed more and larger subcutaneous nodules [9]. The nodules were removed by an orthopedists and complex HP diagnosis was submitted [15]. Subcutaneous RNs examined were found in areas of fibrinoid necrosis and inflammatory cells with radial disposition (Figure 4, a and b).

Fibrinoid necrosis appears as an acellular eosinophil area (Figure 5), anucleate (Figure 6), inflammatory cells surrounded by lymphocytes and histiocytes (Figure 7, a and b).

Immunohistochemistry (IHC): CD68 (macrophage marker) was positive for cytoplasmic membrane of the inflammatory infiltrate in histiocytes (Figures 8 and 9); CD10 (leukocyte common antigen) was positive for cytoplasmic membrane in inflammatory granulocytes (Figure 10), which justifies the initiation of the inflamematory cascade of interleukins; CD45RO (marker for T-lymphocytes) was intense and focal positive in T-lymphocytes that make up the RN (Figure 11); CD20 (B-lymphocyte marker) was negative in inflammatory cells; vimentin (mesenchymal marker) was intensely and diffusely positive in fibroblasts and endothelial cells of the conjunctive-vascular component, and in some macrophages (Figure 12, a–c); cytoplasmic S100 protein was positive in histiocytes of inflammatory infiltrate (Figures 13 and 14).

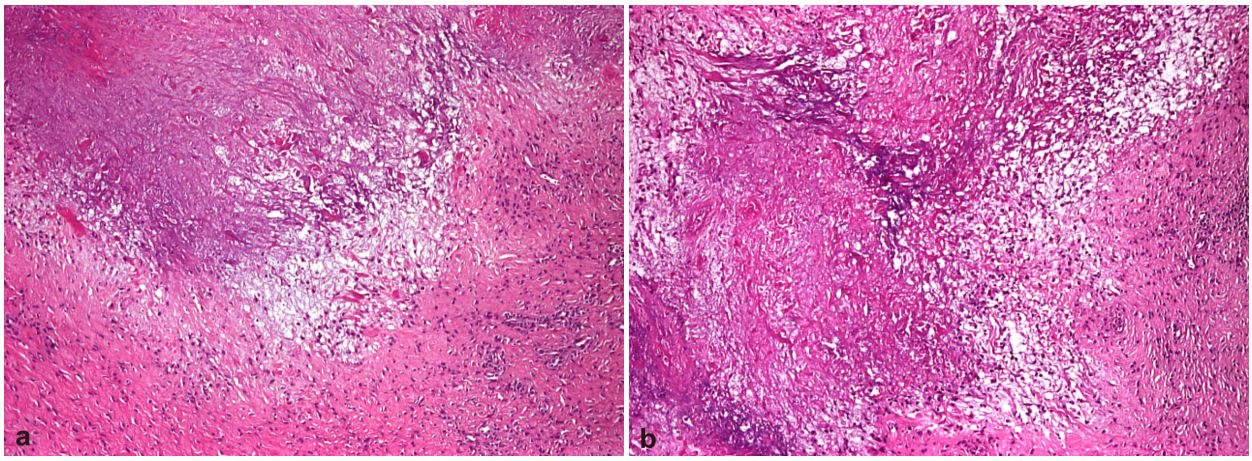

Figure 4 – ***(a) RN represented by fibrinoid necrosis and inflammatory cells with radial disposition; (b) RN presenting central fibrinoid necrosis surrounded by chronic inflammation. HE staining, ×40.***

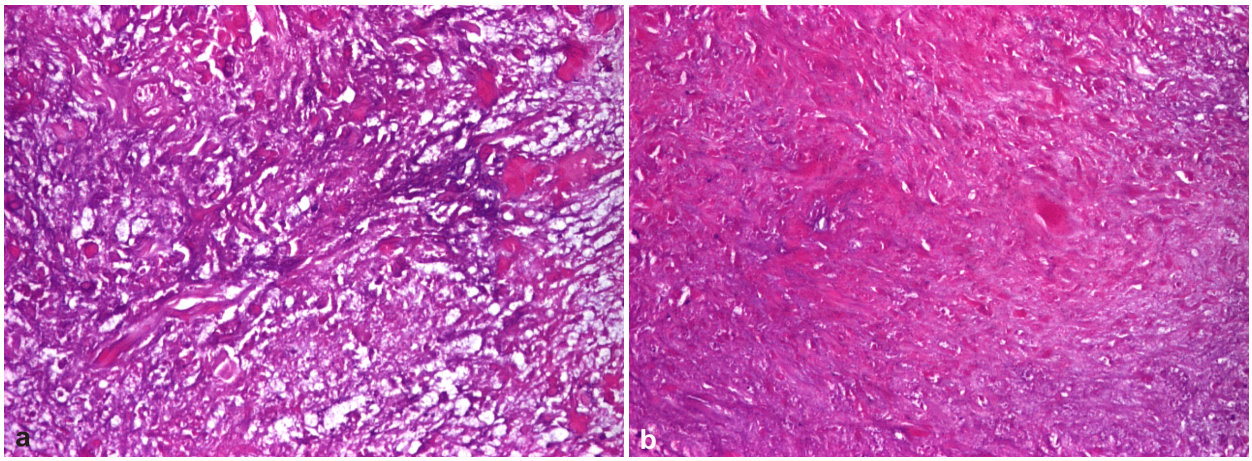

Figure 5 – ***Fibrinoid necrosis: acellular eosinophil area. HE staining,×100.***

Figure 6 – ***Fibrinoid necrosis: anucleate eosinophils,. HE staining,×100.***

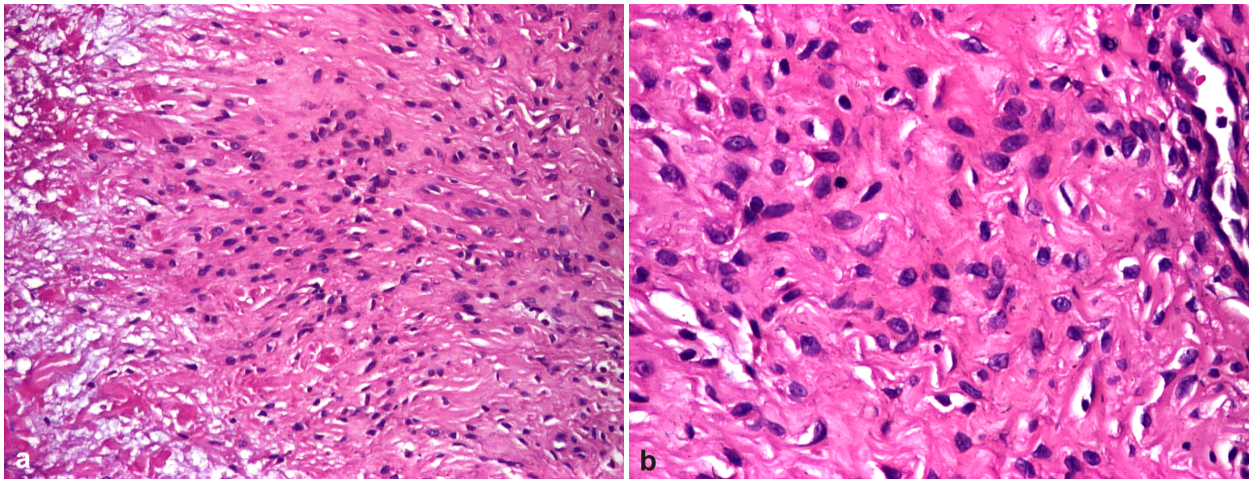

Figure 7 – *(a) RN represented by fibrinoid necrosis surrounded by lymphocytes and histiocytes; (b) Lymphocytes and inflammatory cells represented by histiocytes. HE staining, ×100.*

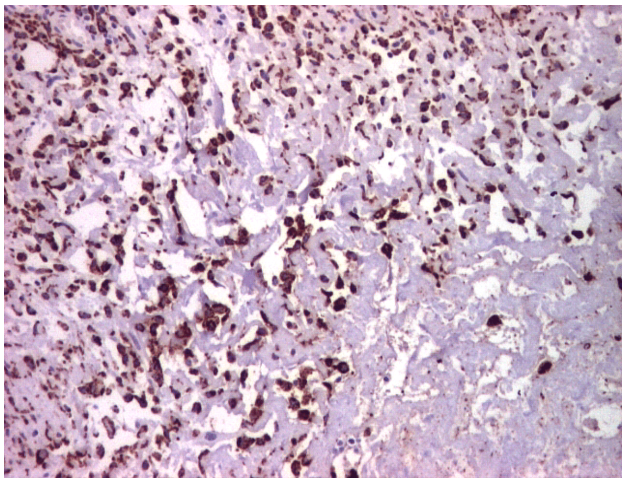

Figure 8 – *RN: intensely and diffuse CD8-positivity of histiocytes. IHC staining, ×100.*

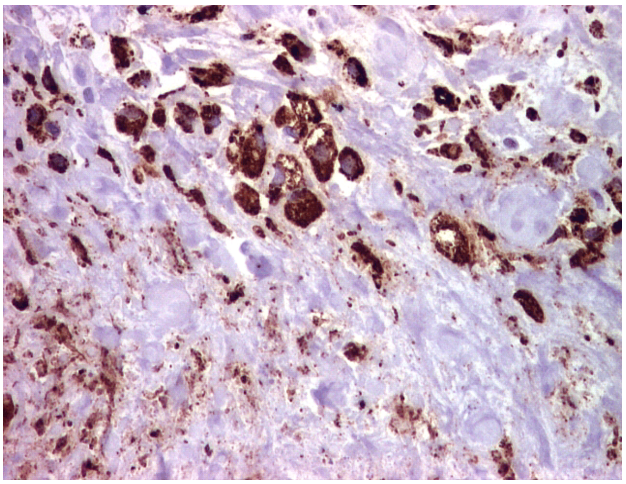

Figure 9 – *RN: CD68-positive cytoplasm and membrane in inflammatory histiocytes. IHC staining, ×200.*

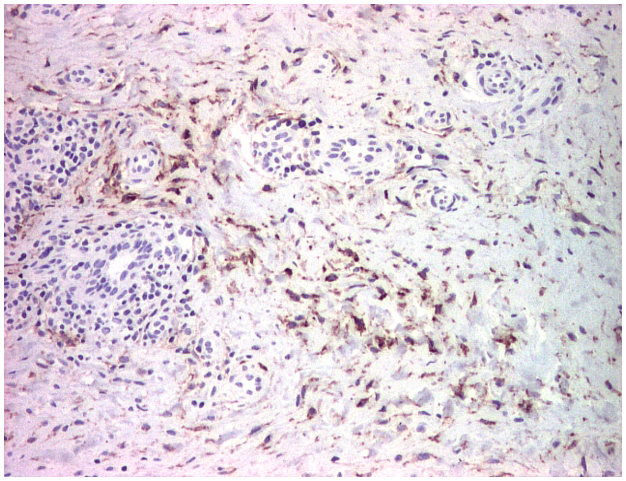

Figure 10 – *RN: CD10-positive cytoplasm and membrane in the granulocytes of the inflammatory infiltrate. IHC staining, ×100.*

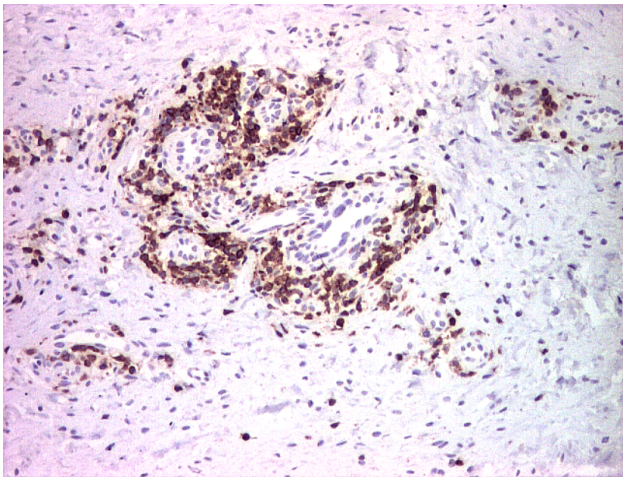

Figure 11 – *RN: intensely and focal CD45RO-positivity at T-lymphocytes membrane level in the inflammatory infiltrate. IHC staining, ×100.*

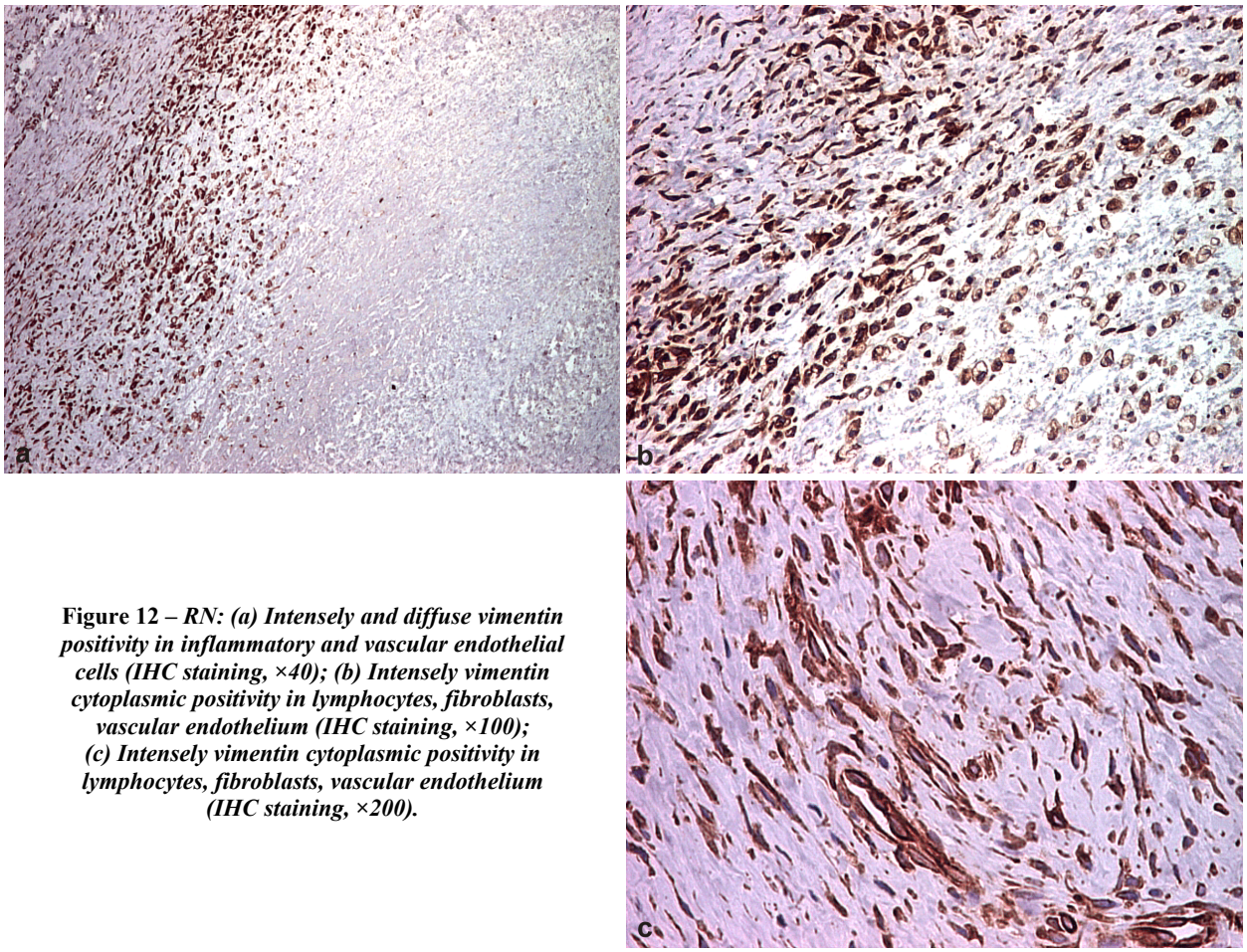

Figure 12 – ***RN: (a) Intensely and diffuse vimentin positivity in inflammatory and vascular endothelial cells (IHC staining, ×40); (b) Intensely vimentin cytoplasmic positivity in lymphocytes, fibroblasts, vascular endothelium (IHC staining, ×100); (c) Intensely vimentin cytoplasmic positivity in lymphocytes, fibroblasts, vascular endothelium (IHC staining, ×200).***

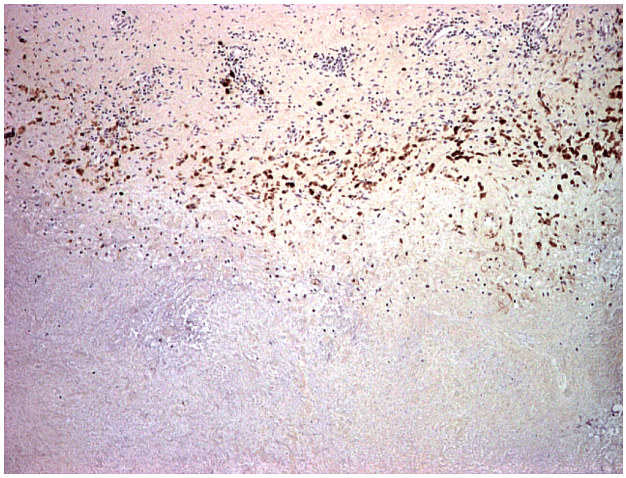

Figure 13 – ***RN: intensely and focal S100 positivity in inflammatory histiocytes. IHC staining, ×40.***

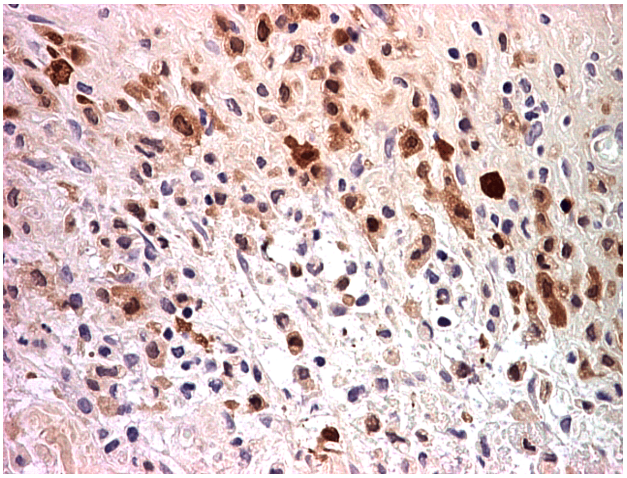

Figure 14 – ***RN: intensely S100 cytoplasmic positivity in inflammatory histiocytes. IHC staining, ×200.***

Discussion

In our study, we made a complex assessment of patients with RA and RN (clinical, functional, imagistic and histological assessment), and we realized a correlation between pain, disability and histological aspect of RN, before and after rehabilitation program. The RA diagnosis was made using the 1987 ACR classification criteria, because we focused on the complex impact of RN in RA patients. New classification criteria for RA do not include presence of rheumatoid nodules or radiographic erosive changes, both of which are less likely in early RA. In general, patients with rheumatoid nodules tend to have a severe RA phenotype, with more rapid progression of joint destruction than other patients with RA. This is the reason of the complex study, which we performed.

Clinical and functional assessment

Medical literature states that in the last decade, RA had a severe impact on the individual's life, with complex consequences for different aspects of patient's quality of life (the physical, social and psychological aspects) [13].

Therefore, we assessed all patients in accordance with the ICF (*International Classification of Functioning, Disability and Health*) framework, based on the causal

cascade [16]. Inflammation of the joints, RN, pain, stiffness and fatigue were present as clinical consequences of RA and its impact on the body functions and structures. The major concern for patients was pain. Although controlling pain is obtained after a complete rehabilitation program, all patients had various degrees of pain despite therapy. Its persistence is an important negative consequence of the disease. Activities and participation for studied females was limited in various degrees and was defined by functionality and disability because of pain, inflammation and joint damage; they had disturbance of fine motor skills (hands, feet, elbows become disfigured). Active joint disease may impair physical function and may also be aggravated by physical activity.

In our study, diagnosis of RN is made clinically. All females in our study had boggy swelling in proximal interphalangeal and metacarpophalangeal joints (more prominent on right hand) and larger mobile nodules in elbows. They were present in the main pressure points: hand, finger and elbow. We took into consideration other subcutaneous masses in differential diagnosis – rheumatoid nodules (in the absence of arthritis), gout tophi, synovial cyst, lipomas, fibromas, subcutaneous granuloma, xanthomas, nodular or keloidal scleroderma, granuloma, basal cell carcinoma, metastatic tumors. No RN caused severe complications, like infections, neuropathy, ulcerations, or fistula formation. All RNs were covered with normal skin [9].

We noted three poor prognostic factors: subcutaneous rheumatoid nodules, positive serum RF findings and positive serum anti-CCP (cyclic citrullinated peptide) autoantibodies [17].

Surgical removal was performed for big RN located in elbow, where they generated pain and limited joint mobility with significant functional impact on the motor skill of the hand complex. These painful nodules interfered with daily activities and limited movements.

We consider that in our study the main factor linked to increased development of RN is Methotrexate treatment. This idea is sustained upon two arguments: first one is the literature data and the second one is the functional status of our patients (RN usually occurs in patients with severe RA but our RA studied females with moderate disease).

We did not assessed the severity of fatigue; patients receiving Methotrexate had higher scores of fatigue and this symptom appears to be related to disease activity, joint structural damage, immunological status and functional disability [18]. Because all studied patients had moderate DAS28 and this parameter was consistently correlated with HAQ, we considered that severity of pain was enough to quantify and monitor the rehabilitation program.

The last two components of ICF framework – environmental factors and personal factors, including psychological status, must be analyzed as contextual factors. We did not follow the psychological impacts.

Global, QoL in RA patients is assessed using various scales, related with pain, disease activity, functional status, and radiological progression [19].

We followed functional status with HAQ, one of the important scales for RA patients, widely used for measurement in clinical studies because it was more sensitive to differences in demographic, lifestyle, and disease- and treatment-related factors than other scales. In our study, HAQ scores have shown to correlate well with both clinical and laboratory measures, including RN [13, 20].

The eight categories of HAQ, reviewing a total of 20 specific functions, evaluated patient difficulty with activities of daily living over the past weeks, before the study. We took into consideration RA patients in the middle functional classes (class II and class III), because we followed the functional gain after the rehabilitation program, so all patients had to able to perform usual self-care activities.

Optimal management of RA involves more than medication (pharmacological therapy). Early in the course of the disorder, the patient need to learn to accept that he or she will be living with RA and will need to become involved in the process of making decisions about any aspect of the complex treatment. An interdisciplinary team (rheumatologist, rehabilitation doctor, physical therapist, occupational therapist, and/or vocational counselor) approach to the comprehensive management of RA. These fundamental recommendations were applied in our patients [21–24].

The rehabilitation program was performed for improvement of clinical and functional status of patients. All females in our study had late-onset disease, with moderate disease activity, with positive rheumatoid factor and anti-citrullinated protein antibody findings, so remission of disease was not possible. Remission is obtained in 10% to 50% of patients with RA, and is more likely in persons younger than 40 years, males, nonsmokers, with shorter duration of disease, with milder disease activity, without elevated acute phase reactants, and without positive rheumatoid factor [25].

We adapted the kinetic program (instruction for joint protection, exercises for joint range of motion, strengthening exercises, aerobic conditioning exercise programs) to the functional status of any patient and to maintaining joint function. The kinetic program goal was to regain all activities of daily living and wellbeing without increasing pain, fatigue or joint symptoms.

Histological assessment

The complexity of clinical and functional aspects is in accordance with immunological cellular cascade described in the rheumatoid nodule and other involved conjunctive structure, especially diarthroidal joints. So, literature data mentions three levels of histological evolution for diarthroidal joint in RA. Initially, there is a synovial and perisynovial inflammatory infiltrate, followed by fibrinoid accumulation. Then, synovial villosities become hypertrophied, a chronic inflammatory infiltrate appears and the proliferation of vascular tunica intima. In the last stage, the inflammation extends to the articular cartilage and subchondral bone, resulting in fibrosis. This joins bone extremities and multiloculates articular cavities [15].

The exact etiology of RN is unknown. It has been hypothesized that a series of events beginning with local trauma are responsible for the development of RNs. A recent study of cytokine composition suggests that the nodule is probably due to a Th-1-mediated inflammatory mechanism [26].

This data suggests that a specific T-cell mediates the immune reaction that occurs in rheumatoid nodules. The precise relation between immune reactions occurring in rheumatoid nodules, on the one hand, and in rheumatoid synovium, on the other, remains unresolved [9].

In the literature data, each RN has a HP progression, including three stages: the first – an acute inflammatory stage; the lesion consists in an area resembling granulation tissue with clusters of newly proliferated capillaries surrounded by undifferentiated mononuclear cells and fibroblasts; the second – a granulomatous stage, with the development of necrosis and palisading of elongated mononuclear cells, macrophages, at the periphery of the initial focus of granulation tissue, the third – a necrotic stage; this final stage begins as the granulation-like tissue develops into a large central focus of necrotic collagen and reticulin fibers, mixed with fibrinoid material, fat cells, lymphocytes, and deposited immunoglobulins [7].

Histologically, all examined rheumatoid nodules are mature nodules and are composed of three formal zones (areas or layers), as are described in medical literature: inner area, represented by a central necrosis, composed of collagen, fibrinoid material, reticular fibers, serum proteins, cellular organelles; the small RN (pea sized RN) has only one necrotic center; the larger RN tends to have multiple necrotic centers, separated through shells or connected (multilocular RN); sometimes, when RN are nearly a diarthroidal joint, the necrotic centers may open to a large bursal pocket containing synovial fluid. Uncommonly, in the center of necrobiotic areas, it may be evidence of a necrotic blood vessel associated with nuclear fragments or sparse neutrophils, in correlation with an acute vasculitis in the surrounding vessels of RN [7, 27]; middle area or palisading is a densely packed layer (cellular palisade), is a really boundary between the inner area and the outer zone and gives the characteristic feature of the nodule; it contains mononuclear cells (*e.g.*, T-lymphocytes, monocytes, macrophages, fibroblasts); monocytes migrating from outer zone blood vessels to the inner zone, with the phenotype particular changing to activated macrophages as they travel; these macrophages are stain positive, HLA-DR positive and generate macrophage specific antibodies; macrophages and fibroblasts tend to be arranged radially, like the seeds of a fig [28]. The functions of these cells, their ability to present antigens to T-cells, were studied in the last decades. It is mentioned that interleukin-1, the first step of the cascades or networks of cytokines, in both rheumatoid nodules and rheumatoid synovium, produced locally by these cells induces the proliferation of fibroblasts, which in turn promotes palisade formation in the middle layer of RN [29]; outer area, like a fibrous shell, represented by vessels and perivascular infiltration of chronic inflammatory cells (lymphocytes and plasma cells).

Old lesions of RN show extensive fibrosis in which clefts and cystic degeneration of the necrobiosis foci persist [30]. Nodules also may contain significant amounts of lipids and cholesterol that are released into adjacent bursae and lead to milky bursal effusions, known as rheumatoid chyliform bursitis [31]. This description confirms the including RN in the group of necrobiotic nodules (rheumatoid nodule, subcutaneous granulomas annulare, and necrobiosis lipoidica).

These nodules have a common HP characteristic – a central region of fibrinoid necrosis (necrosed collagen), a middle region represented by a palisade of elongated histiocytic cells, and an outer region of granulation tissue with fibrosis, plasma cells, lymphocytes, and possibly giant cells [32].

A through histochemical study can distinguish the RN of subcutaneous granulomas annulare and make an accurate diagnosis and choice right treatment [RN tended to present homogeneous, eosinophilic necrobiosis, giant cells within palisaded foci and significant stromal fibrosis, while subcutaneous granuloma annulare (SGA) lesions demonstrated pale, edematous necrobiosis, an absence of giant cells, and lesser degrees of fibrosis] [32].

In the cellular cascade, the T-lymphocyte has a special role. This aspect is justified by the results obtained through IHC examination. CD20 marker staining was negative for B-lymphocytes, unlike the CD45RO marker for T-lymphocytes, which was intensely positive. The role of T-lymphocytes in the pathogenesis of rheumatoid arthritis is still debated but generally accepted. IHC staining of infiltrating lymphocytes with T-cell receptor specific monoclonal anti-idiotypic antibodies showed a polyclonal T-cell population with VP representation comparable with that in peripheral blood lymphocytes. Also, we described a specific T-cell mediated immune reaction that occurs in rheumatoid nodules.

T-lymphocytes are found in variable numbers, distributed among the macrophages and more importantly, in the area surrounding the palisaded mononuclear cells, where they are concentrated around small vessels. These lymphocytes are mainly CD3-positive T-lymphocytes. Only a minority of these infiltrating lymphocytes seem to be activated, as indicated by the low expression of interleukin-2 (IL-2) receptor (expressed by 1% or less of infiltrating T-lymphocytes). The low expression of IL-2 receptor among lymphocytes in situ was confirmed [33].

In our immunohistologically study, through vimentin highlight (mesenchymal marker), intensely positive in fibroblasts and the endothelial cells of the vascular-conjunctive component, we can confirm one of the factors responsible for the pathogenesis of the RN: trauma to small blood vessels at pressure points, causing local pooling of immune complexes. Also, CD68 (macrophage marker), intensely positive in the cytoplasm and membrane of the histiocytes from the inflammatory infiltrate confirms the activation of macrophage by immune complexes.

The other factors involved in the RN pathogenesis are: genetic predisposition associated with HLA and TNF polymorphisms; cytokines – production of pro-inflammatory cytokines and tissue necrosis by cytokines; tissue necrosis by proteinases and collagenases [29].

These histological aspects are similar to that of rheumatoid synovitis with the main differences being that the palisade area replaces the synovial intima (they may blend imperceptibly in bursae) and an almost total absence of B-lymphocytes [34].

Conclusions

RA patients remain a real challenge for any medical team, which strives for complete medical assistance (medications and rehabilitative techniques) for increasing the quality of life, decreasing the potential long-term disabilities and obtain patient functional independence. Complete assessment of RA patients with RN permits for the medical assistance quantification, also the patient has a poor evolution prognosis. Immunohistological complexity of RN reflects the intensity of inflammatory–immune process and the gravity of interleukin networks. Future studies should elucidate the relations between immune reactions occurring in RNs, on the one hand, and in rheumatoid synovium, on the other, both aspects with final impact on the patient quality of life.

Conflict of interests

The authors declare that they have no conflict of interests.

References

[1] Suissa S, Ernst P, Hudson M, Bitton A, Kezouh A. Newer disease-modifying antirheumatic drugs and the risk of serious hepatic adverse events in patients with rheumatoid arthritis. Am J Med, 2004, 117(2):87–92.

[2] Scott DL, Wolfe F, Huizinga TW. Rheumatoid arthritis. Lancet, 2010, 376(9746):1094–1108.

[3] American College of Rheumatology Subcommitee on Rheumatoid Arthritis Guidelines. Guidelines for the management of rheumatoid arthritis: 2002 update. Arthritis Rheum, 2002, 46(2):328–346.

[4] Bălănescu A. Poliartrita reumatoidă: de la patogenie la clinică. Ed. Medicală Amaltea, Bucureşti, 2007, 15, 16, 109, 110.

[5] Alamanos Y, Voulgari PV, Drosos AA. Incidence and prevalence of rheumatoid arthritis, based on the 1987 American College of Rheumatology criteria: a systematic review. Semin Arthritis Rheum, 2006, 36(3):182–188.

[6] Gordon MM, Hampson R, Capell HA, Madhok R. Illiteracy in rheumatoid arthritis patients as determined by the Rapid Estimate of Adult Literacy in Medicine (REALM) score. Rheumatology (Oxford), 2002, 41(7):750–754.

[7] García-Patos V. Rheumatoid nodule. Semin Cutan Med Surg, 2007, 26(2):100–107.

[8] Nyhäll-Wåhlin BM, Turesson C, Jacobsson LT, Nilsson JÅ, Forslind K, Albertsson K, Rönnelid J, Petersson IF. The presence of rheumatoid nodules at early rheumatoid arthritis diagnosis is a sign of extra-articular disease and predicts radiographic progression of joint destruction over 5 years. Scand J Rheumatol, 2011, 40(2):81–87.

[9] Veys EM, De Keyser F. Rheumatoid nodules: differential diagnosis and immunohistological findings. Ann Rheum Dis, 1993, 52(9):625–626.

[10] Neogi T, Aletaha D, Silman AJ, Naden RL, Felson DT, Aggarwal R, Bingham CO 3rd, Birnbaum NS, Burmester GR, Bykerk VP, Cohen MD, Combe B, Costenbader KH, Dougados M, Emery P, Ferraccioli G, Hazes JM, Hobbs K, Huizinga TW, Kavanaugh A, Kay J, Khanna D, Kvien TK, Laing T, Liao K, Mease P, Ménard HA, Moreland LW, Nair R, Pincus T, Ringold S, Smolen JS, Stanislawska-Biernat E, Symmons D, Tak PP, Upchurch KS, Vencovský J, Wolfe F, Hawker G; American College of Rheumatology; European League Against Rheumatism. The 2010 American College of Rheumatology/European League Against Rheumatism classification criteria for rheumatoid arthritis: Phase 2 methodological report. Arthritis Rheum, 2010, 62(9):2582–2591.

[11] Hochberg MC, Chang RW, Dwosh I, Lindsey S, Pincus T, Wolfe F. The American College of Rheumatology 1991 revised criteria for the classification of global functional status in rheumatoid arthritis. Arthritis Rheum, 1992, 35(5):498–502.

[12] Wells G, Becker JC, Teng J, Dougados M, Schiff M, Smolen J, Aletaha D, van Riel PL. Validation of the 28-joint Disease Activity Score (DAS28) and European League Against Rheumatism response criteria based on C-reactive protein against disease progression in patients with rheumatoid arthritis, and comparison with the DAS28 based on erythrocyte sedimentation rate. Ann Rheum Dis, 2009, 68(6):954–960.

[13] Maska L, Anderson J, Michaud K. Measures of functional status and quality of life in rheumatoid arthritis: Health Assessment Questionnaire Disability Index (HAQ), Modified Health Assessment Questionnaire (MHAQ), Multidimensional Health Assessment Questionnaire (MDHAQ), Health Assessment Questionnaire II (HAQ-II), Improved Health Assessment Questionnaire (Improved HAQ), and Rheumatoid Arthritis Quality of Life (RAQoL). Arthritis Care Res (Hoboken), 2011, 63(Suppl 11):S4–13.

[14] Bojinca V, Janta I. Rheumatic diseases and malignancies. Maedica (Buchar), 2012, 7(4):364–371.

[15] Simionescu C, Mărgăritescu C, Foarfă C, Ciurea R, Stepan A. Morfopatologie generală – curs. Ed. Medicală Universitară, Craiova, 2011, 137.

[16] Pollard L, Choy EH, Scott DL. The consequences of rheumatoid arthritis: quality of life measures in the individual patient. Clin Exp Rheumatol, 2005, 23(5 Suppl 39):S43–S52.

[17] Majithia V, Geraci SA. Rheumatoid arthritis: diagnosis and management. Am J Med, 2007, 120(11):936–939.

[18] Ibn Yacoub Y, Amine B, Laatiris A, Wafki F, Znat F, Hajjaj-Hassouni N. Fatigue and severity of rheumatoid arthritis in Moroccan patients. Rheumatol Int, 2012, 32(7):1901–1907.

[19] Garip Y, Eser F, Bodur H. Health-related quality of life in rheumatoid arthritis: comparison of RAQoL with other scales in terms of disease activity, severity of pain, and functional status. Rheumatol Int, 2011, 31(6):769–772.

[20] Linde L, Sørensen J, Østergaard M, Hørslev-Petersen K, Rasmussen C, Jensen DV, Hetland ML. What factors influence the health status of patients with rheumatoid arthritis measured by the SF-12v2 Health Survey and the Health Assessment Questionnaire? J Rheumatol, 2009, 36(10):2183–2189.

[21] Bell MJ, Lineker SC, Wilkins AL, Goldsmith CH, Badley EM. A randomized controlled trial to evaluate the efficacy of community based physical therapy in the treatment of people with rheumatoid arthritis. J Rheumatol, 1998, 25(2):231–237.

[22] Komatireddy GR, Leitch RW, Cella K, Browning C, Minor M. Efficacy of low resistance muscle training in patients with rheumatoid arthritis functional class II and III. J Rheumatol, 1997, 24(8):1531–1539.

[23] Neuberger GB, Press AN, Lindsley HB, Hinton R, Cagle PE, Carlson K, Scott S, Dahl J, Kramer B. Effects of exercise on fatigue, aerobic fitness, and disease activity measures in persons with rheumatoid arthritis. Res Nurs Health, 1997, 20(3):195–204.

[24] Van den Ende CH, Vliet Vlieland TP, Munneke M, Hazes JM. Dynamic exercise therapy in rheumatoid arthritis: a systematic review. Br J Rheumatol, 1998, 37(6):677–687.

[25] Britsemmer K, Ursum J, Gerritsen M, van Tuyl L, van Schaardenburg D. Validation of the 2010 ACR/EULAR classification criteria for rheumatoid arthritis: slight improvement over the 1987 ACR criteria. Ann Rheum Dis, 2011, 70(8):1468–1470.

[26] Hessian PA, Highton J, Kean A, Sun CK, Chin M. Cytokine profile of the rheumatoid nodule suggests that it is a Th1 granuloma. Arthritis Rheum, 2003, 48(2):334–338.

[27] Sayah A, English JC 3rd. Rheumatoid arthritis: a review of the cutaneous manifestations. J Am Acad Dermatol, 2005, 53(2):191–209; quiz 210–212.

[28] Kato H, Yamakawa M, Ogino T. Complement mediated vascular endothelial injury in rheumatoid nodules: a histopathological and immunohistochemical study. J Rheumatol, 2000, 27(8): 1839–1847.

[29] Ziff M. The rheumatoid nodule. Arthritis Rheum, 1990, 33(6): 761–767.

[30] Nihei Y. Cutaneous mucinous nodules associated with proliferating synovitis of rheumatoid arthritis. J Dermatol, 1999, 26(4):229–235.

[31] Taccari E, Teodori S. Rheumatoid chyliform bursitis: pathogenic role of rheumatoid nodules. Arthritis Rheum, 1984, 27(2): 221–226.
[32] Kim S, Parker WL, Beckenbaugh RD. Atypical rheumatoid nodules: a possible precursor to a rheumatoid variant in a rheumatoid-factor-negative patient. Case report. Hand (N Y), 2009, 4(1):62–65.
[33] Miyasaka N, Sato K, Yamamoto K, Goto M, Nishioka K. Immunological and immunohistochemical analysis of rheumatoid nodules. Ann Rheum Dis, 1989, 48(3):220–226.
[34] Carmona L, González-Alvaro I, Balsa A, Angel Belmonte M, Tena X, Sanmartí R. Rheumatoid arthritis in Spain: occurrence of extra-articular manifestations and estimates of disease severity. Ann Rheum Dis, 2003, 62(9):897–900.

Corresponding author
Magdalena-Rodica Trăistaru, Associate Professor, MD, PhD, Department of Physical Medicine and Rehabilitation, University of Medicine and Pharmacy of Craiova, 2 Petru Rareş Street, 200349 Craiova, Romania; Phone +40723–766 778, e-mail: rodicatraistru@hotmail.com

Received: July 18, 2015

Accepted: April 29, 2016