

## Clinical and Morphological Aspects of Sinovitis in Early Rheumatoid Arthritis

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**ABSTRACT** The earliest joint changes in rheumatoid arthritis occur in the synovial membrane, leading to development of an un-suppurated proliferative synovitis. This study is based on 33 cases of early rheumatoid arthritis for which we have investigated a series of clinical and morphological parameters. For the examined cases we found that the disease incidence reached its maximum in fifth and sixth decades of life, predominantly in females, over half of cases being diagnosed in the first six months from the onset of the disease. Histopathological study of synovial membrane samples showed characteristic morphological changes but unspecific for the disease, represented by the synoviocytes proliferation, inflammatory infiltrates, fibrinoid necrosis, fibroblasts proliferation and vascular changes. Reaching composite histological score may be useful by providing some information on the severity of the disease.

**KEY WORDS** early rheumatoid arthritis, clinic, histopathology

### Introduction

Synovial lesions in rheumatoid arthritis indicate a complex of histopathological aspects useful in disease severity diagnosis. Morphologically, joint inflammation in rheumatoid arthritis begins with synovial membrane and extends to the cartilage and subchondral bone level, eventually leading to destructive changes of the joint. This feature clearly differentiates rheumatoid arthritis from osteoarthritis that starts at the joint level and in which the synovial membrane is secondarily affected, and some septic arthritis in which the first change in the bone marrow (1, 2). In early rheumatoid arthritis first changes occur in the synovial membrane, developing furthermore an un-suppurated proliferating synovitis. At the onset of illness, for a short period of time, acute inflammatory changes occur. If the process continues, the acute inflammatory response is rapidly replaced by chronic inflammation that is characteristic to rheumatoid synovitis. Thus, if at the beginning, the synovitis type is exudative, it quickly progresses to a proliferative - infiltrative appearance (7, 8, 9).

### Materials and Methods

The present paper is a retrospective study of a period of two years (2009-2010), that allowed us to select a cohort of 33 cases of early rheumatoid arthritis in its first year after onset. We used as study material human tissue represented by biopsy fragments obtained from endoscopic puncture of the knee joint from patients hospitalized in the Clinic of Orthopedics and Traumatology, Clinical

Emergency Hospital Craiova. Biopsical fragments were processed by conventional histological technique and diagnosed in the same hospital.. Clinical data of studied patients included: gender, patient age, clinical diagnosis and the time since the onset of disease. Histopathological analysis assessed the synoviocytes proliferation severity, the presence of inflammatory infiltrate, the presence of fibrinoid necrosis, the fibroblasts proliferation and vascular changes, marking each one with a degree of severity. Then we calculated the composite histological score that we have correlated with clinical data in the study.

### Results

The analysis of the 33 cases of early rheumatoid arthritis showed that most cases were diagnosed in the fifth and sixth decades of life, during which we have found a number of 12 and 14 cases respectively, these cases representing 78,7% of the entire lot. The youngest patient was 32 years old and the oldest 58 years.

Caseload distribution based on gender showed the predominance of the disease in women with 26 cases, representing 78.8% of the total caseload, compared to males that we have found only 7 cases, representing 21.2% of analyzed cases. We can say with certainty that in this study, the disease was 2.6 times more common in females than in males.

In terms of time elapsed since the onset of disease we have taken into account only the patients diagnosed during the first year of illness. Most patients admitted in our study, 24 cases

(72.7%) were diagnosed during the first six months from the onset of the disease. Maximum incidence of this diagnosis ranged between 6 - 7 months, in which we have found 10 cases (30.3%).

The synoviocytes proliferation was constantly present, varying from under 3 to 10 layers, most cases corresponding to a score equal to 2 (8 cases - 24.2%). Thus, depending on the extent of the synoviocytes proliferation, we have found: 1<sup>st</sup> degree in 5 cases (15.2%) with  $\leq 3$  rows of synoviocytes proliferation, 2<sup>nd</sup> degree in 8 cases (24.2%) with synoviocytes proliferation in 3-4 rows, 3<sup>rd</sup> degree in 11 cases (33.3%) synoviocytes proliferating in 5-6 rows, 4<sup>th</sup> degree in 9 cases (27.3%) with the synoviocytes proliferation  $\geq 6$  rows (fig. 1).

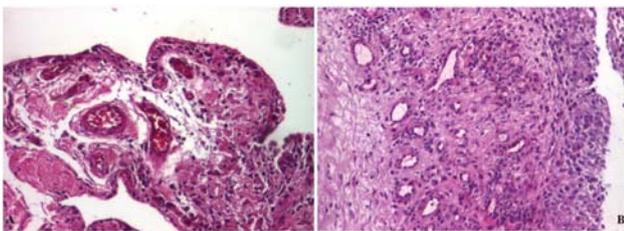


Figure 1. Rheumatoid arthritis, synoviocytes proliferation, HE stain; A. Grade 2 (3-4 rows), x40; B. Grade 4 ( $\geq 6$  rows), x100

Depending on the intensity of the fibroblasts proliferation we have classified the 33 cases of early rheumatoid arthritis in the following degrees of severity: 0 degree in 6 cases (18.2%), with the absence of fibroblasts proliferation, 1<sup>st</sup> degree in 12 cases (36.4%) with mild proliferation of fibroblasts, 2<sup>nd</sup> degree in 8 cases (24.2%) with moderate proliferation of fibroblasts, sometimes with palisade arrangement, 3<sup>rd</sup> degree in 7 cases (21.2%) with intense fibroblast proliferation and pseudotumoral aspects (fig. 2).

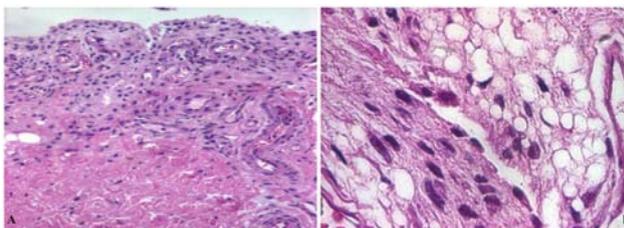


Figure 2. Rheumatoid arthritis, fibroblasts proliferation, HE stain; A. Mild proliferation, x100; B. Intense fibroblast proliferation, x200

We have also appreciated the appearance and severity of inflammatory infiltrate. Analyzing the intensity of inflammatory infiltrate in order of frequency we found the following aspects: 1<sup>st</sup> degree in 31 cases (63.6%) that had a reduced lymphoplasmacitary inflammatory infiltrate presenting as perivascular aggregates, 2<sup>nd</sup> degree in 7 cases ( 21.2%) with inflammatory infiltrates forming lymphoid follicles, 3<sup>rd</sup> degree in 3 cases (9.1%) with a diffuse or follicular disposition of

the inflammatory infiltrates, 4<sup>th</sup> degree in 2 cases (6.1%) in which we have noticed the presence of rare multinucleated giant cells, besides the described aspects (fig. 3).

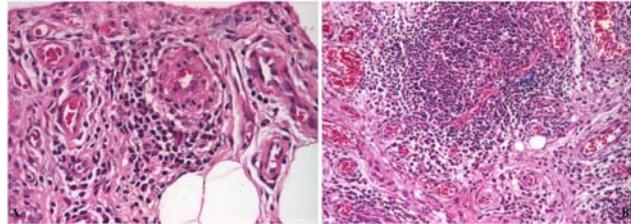


Figure 3. Rheumatoid arthritis, HE stain; A. Perivascular inflammatory aggregate (grade 1), x200; B. Inflammatory infiltrates forming lymphoid follicles (grade 3), x100

Analyzing the cases studied in terms of fibrinoid necrosis extent, we observed that they corresponded to: 0 degree in 11 cases (33.3%) with absent fibrinoid necrosis, 1<sup>st</sup> degree in 8 cases (24.3%) with several focal areas of fibrinoid necrosis, 2<sup>nd</sup> degree in 7 cases (21.2%) with extensive fibrinoid necrosis extent and 3<sup>rd</sup> degree in 7 cases (21.2%) in which fibrinoid necrosis was diffusely present with a necrosis "band" (fig. 4).

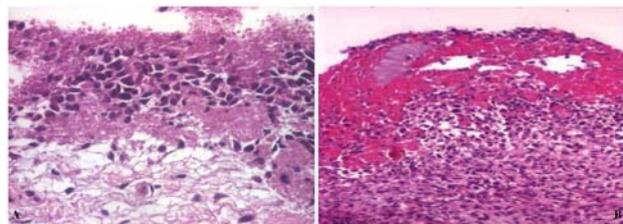


Figure 4. Rheumatoid arthritis, fibrinoid necrosis, HE stain; A. Extensive fibrinoid necrosis (grade 2), x100; B. Diffusely fibrinoid necrosis (grade 3), x40.

Depending on the severity of vascular changes we found: 1<sup>st</sup> degree in 2 cases (27.3%) with pronounced vasodilation of subsynviocytes blood vessels (Figure 5), 2<sup>nd</sup> degree in 7 cases (24.2%), in which there was also hematic extravasation or increased number of subsynviocytes vessels near the vasodilation, 3<sup>rd</sup> degree in 14 cases (21.2%), with increased of the number of subsynviocytes vessels, 4<sup>th</sup> degree in 8 cases (27.3%) in which we observed a vascular endothelial proliferation and microthrombosis (fig. 5).

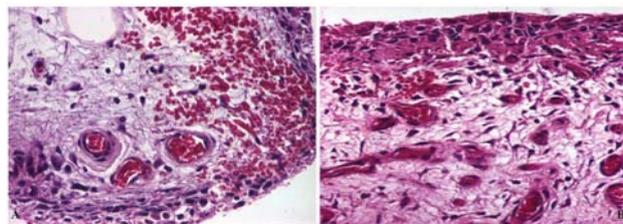


Figure 5. Vascular changes in rheumatoid arthritis, HE stain; A. Vasodilation and hematic extravasation (grade 2), x100; B. Increased of the subsynviocytes vessels number (grade 3), x100.

Degrees for each part of morphological change were necessary to achieve a composite histological score (Table 1):

**Table 1: Casels distribution based on composite histological score**

Composite Histological Score	5-6	7-8	9-10	10-11	12-13	14-15	16-17	17-18
No. of cases	4	5	7	7	5	2	2	1
Percent %	12,1	15,2	21,2	21,2	15,2	6,1	6,1	3

## Discussions

Similar data from literature regarding age groups shows a 1-3% disease frequency for the general population, most patients presenting themselves to a specialist consultation between 35-45 years old (11, 12). The incidence of the disease is estimated at 95-150 new cases annually per 100,000 inhabitants (13, 14).

In our study, the disease affected 2.6 times more frequently the females than males. Data provided by other authors regarding the gender distribution are similar to those found here, most authors indicate a sex ratio of disease of 2.5 / 1 for women / men (3,4), approximately 70% of the patients being women (15, 16).

One of the selection criteria for patients was related to elapsed time since the onset of disease. The term of "early rheumatoid arthritis" is reserved for patients with joint symptoms lasting for less than 12 months. Therefore, we considered only a number of 33 patients diagnosed during the first year after the disease onset.

The earliest changes occur in the synovial membrane, leading in time to an un-suppurated proliferative synovitis. Synovial cell proliferation process occurs both in surface and in its depth. The proliferation and their volume increase leads in time to a net multi-stratification, thickened synovial membrane being coated by 3-5 to 10 rows of hypertrophic synovial cells. In our study, the sinoviocitys proliferation was constantly present, varying from less than 3 layers to 10 layers, but most cases received 2<sup>nd</sup> score (24.2%), corresponding to a proliferation on 4-5 layers.

In our study, the intensity of the inflammatory infiltrate varied from its absence to heavy infiltration with diffuse or follicular disposal, in which we have noticed the presence of some rare giant multinucleated cells, but most often they were reduced, appearing as inflammatory aggregates arranged around the blood vessels.

Lymphocytes are the dominant inflammatory cell population of the rheumatoid arthritis. At first they are near the surface of synovium, diffusely arranged or grouped in small foci centered or not by a blood vessel, forming Allison-Ghormley nodules. In more advanced forms of the disease can be seen abundant lymphocytic infiltrates,

grouped as nodules which, in advanced stages, can form the classic appearance of lymphoid follicles with the presence of germ centers (1, 4, 5). Although they appear later, plasma cells from synovial infiltrate gradually increase in number. They include Russell corpuscles, structures that are the morphological indicator of local synthesis of immunoglobulins (rheumatoid factor), which is a characteristic of rheumatoid synovitis (1, 4, 5, 7).

Rarely, we can observe also macrophage multinucleated cells like foreign body giant cells, having a dispersed arrangement. Macrophages constitute approximately 5-10% of inflammatory population, grouped in lymphoid follicles beside lymphocytes. They are disposed in small groups around small blood vessels in the deep stroma. Rarely, multinucleated giant cells can also be observed, in particular between the layers of proliferated synoviocytes, after fibrin exudation (5, 6).

Fibrinoid necrosis is often present on patients with early rheumatoid arthritis. It can have different spread and depth reported to the coating synoviocytes. The fibrinoid can be seen on the synovial surface that sometimes is covered almost completely. The fibrinoid covers both hypertrophied synoviocytes and stratified ones, passing between them, and especially the synovial ulcerated areas. Under the fibrin layer that remains intact over a period of time, synovial cells proliferate continuously. The analysis of the 33 cases showed that fibrinoid necrosis was mostly absent and when it was present, it had a focal, zonal or diffuse disposition, looking like a "band" necrosis.

Synovial stromal fibroblasts are hypertrophied, increased as a number, arranged in dense cellular groups. In rare cases, the proliferation of synovial stroma may be excessive, forming pseudotumoral aspects "tumor-like proliferation" (5, 6). For the examined cases, when it was present, the fibroblast proliferation had a reduced, moderate or even severe intensity, forming pseudotumoral aspects.

For the 33 analyzed cases we have quantified the appearance of vascular changes depending on the presence of one or more associated changes: congestion, increased number of vessels superficially located, under the coating synoviocytes, erythrocyte extravasation, proliferation of endothelium in arterioles and postcapillary venules.

The first synovial changes occur in the microcirculation, synovium being highly congested, small-caliber blood vessels being focal

or segmental dilated, and present aspects of leukocyte margination and diapedesis. Some vessels are containing thrombi and occasionally small perivascular hemorrhagic foci are present. As a result of vascular congestion and hyperpermeability, the exsudation occurs and is more intense in areas of cartilage margins, near the sinovial-cartilage junction, a process with the participation of endothelial cells of arterioles and venules. Small blood vessels of the synovium and postcapillary venules in particular, appear coated by high endothelial cells, swollen, similar to those found in lymphoid structures. In extreme cases, hypertrophy of endothelial cells may be so pronounced that it determines vascular lumen occlusion (3, 8, 9, 10).

Composite histological score value varied in very wide limits, ranging between 5 and 18. It can provide information on disease severity, but we couldn't make any correlation between composite histological score and the disease onset or age of patients, probably due to the very different morphological aspects.

## Conclusions

The study, which included a total of 33 cases of early rheumatoid arthritis, selected in a 2-year period (2009-2010) demonstrated that most cases of early rheumatoid arthritis were diagnosed in the age range included in the fifth and sixth decades of life (78,7%). The ratio based on gender was in favor of females, with 78.8% of cases studied. As regards the period of disease onset, there were 72.7% of patients diagnosed in the first half year after the onset of disease. Histopathological study of synovium samples from patients with early rheumatoid arthritis showed morphological changes that are characteristic but not specific to the disease, some of them almost constant present, and represented by: synoviocytes proliferation, inflammatory infiltrates, fibrinoid necrosis, proliferation of fibroblasts and vascular changes. The computing of composite histological score can provide useful information on the disease severity, but no correlation with the period of its onset or age of the patients.

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