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Significance of bone marrow edema in pathogenesis of rheumatoid arthritis

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Summary

Assessing the pathology of the synovium, its thickening and increased vascularity through ultrasound and magnetic resonance examinations (more often an ultrasound study alone) is still considered a sensitive parameter in the diagnosis of rheumatoid arthritis and in monitoring of treatment efficacy. Magnetic resonance studies showed that, aside from the joint pannus, the subchondral bone tissue constitutes an essential element in the development of rheumatoid arthritis. Bone marrow edema correlates with inflammation severity, joint destruction, clinical signs and symptoms of rheumatoid arthritis, and thus is considered a predictor of rapid radiological progression of the disease. The newest studies reveal that bone marrow edema may be a more sensitive indicator of the response to therapy than appearance of the synovium. Bone marrow edema presents with increased signal in T2-weighted images, being most visible in fat saturation or IR sequences (STIR, TIRM). On the other hand, it is hypointense and less evident in T1-weighted images. It becomes enhanced (hyperintense) after contrast administration. Histopathological studies confirmed that it is a result of bone inflammation (osteitis/osteomyelitis), i.e. replacememt of bone marrow fat by inflammatory infiltrates containing macrophages, T lymphocytes, B lymphocytes, plasma cells and osteoclasts. Bone marrow edema appears after a few weeks from occurrence of symptoms and therefore is considered an early marker of inflammation. It correlates with clinical assessment of disease activity and elevated markers of acute inflammatory phase, i.e. ESR and CRP. It is a reversible phenomenon and may become attenuated due to biological treatment. It is considered a "herald" of erosions, as the risk of their formation is 6-fold higher in sites where BME was previously noted

Key words: rheumatoid arthritis • pathogenesis • radiography • ultrasonography • magnetic resonance imaging • bone marrow edema

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Background

Assessing the pathology of the synovium, its thickening and increased vascularity through ultrasound and magnetic resonance examinations (more often the ultrasound study alone) is still considered a sensitive parameter in the diagnosis of rheumatoid arthritis and in monitoring of treatment efficacy. Magnetic resonance studies showed that, aside from the joint pannus, the subchondral bone tissue constitutes an essential element in the development of rheumatoid arthritis. Bone marrow edema correlates with inflammation severity, joint destruction, clinical signs and symptoms of rheumatoid arthritis, and thus is considered a predictor of rapid radiological progression of the disease. The newest studies reveal that bone marrow edema may be a more sensitive indicator of the response to therapy than appearance of the synovium [1,2].

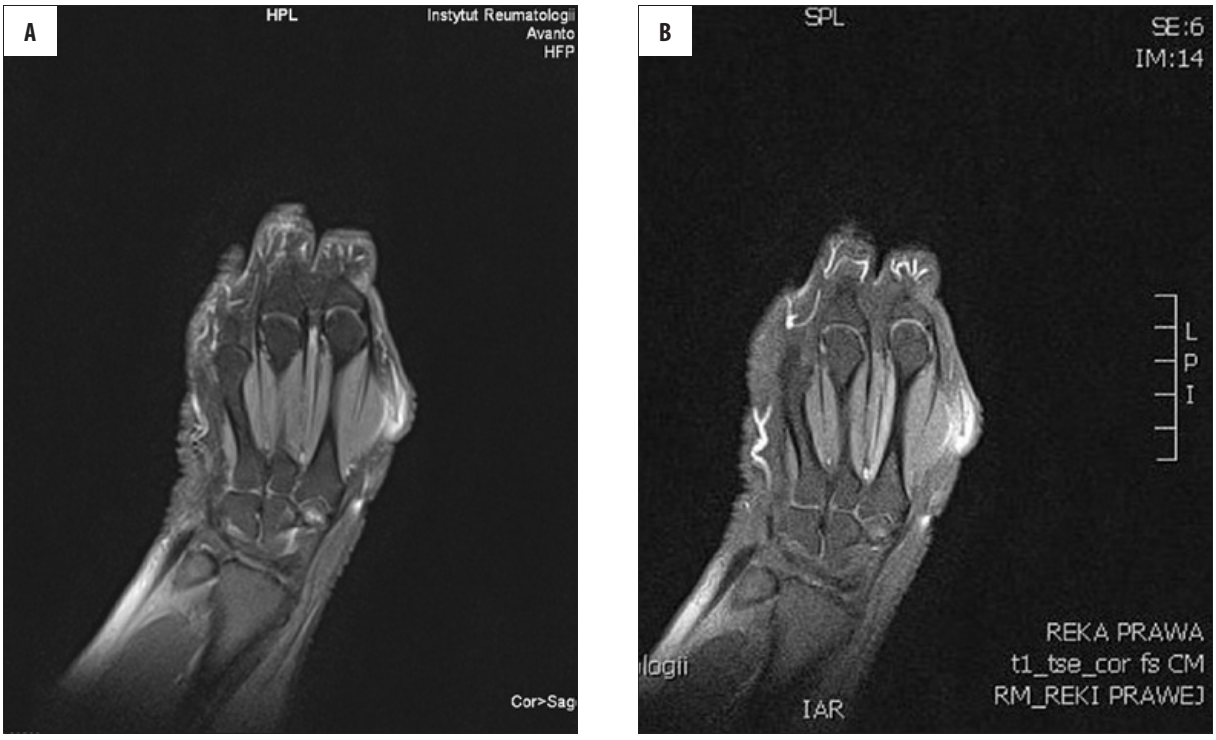
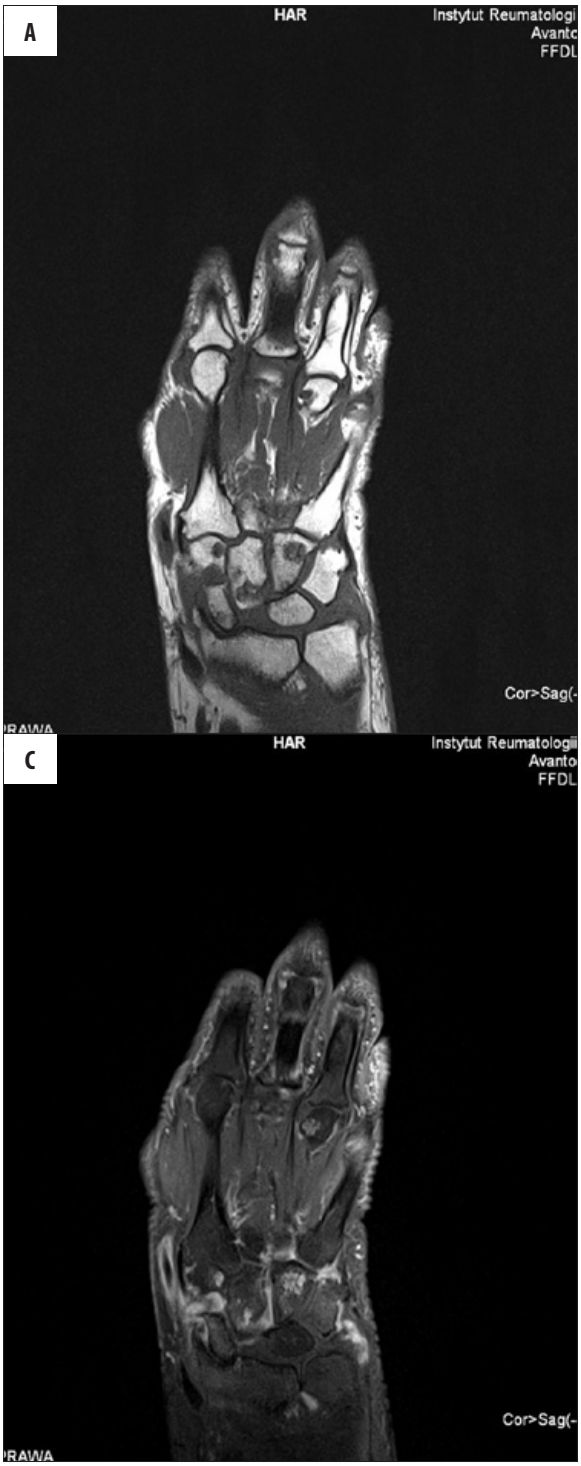


Figure 1. MRI examination: (**A**) PD FS and (**B**) T1 FS CE – showing BME in the trapezoid bone, a small area of BME in the adjacent capitate bone. There is a minor effusion in the mediocarpal joint.

It has long been known that hematopoetic cells constitute bone marrow. However, knowledge that anti-infective immune response begins within the bone marrow, in other words, that bone marrow is also a secondary lymphatic organ, is fairly recent. The newest studies show that bone marrow is important for pathogenesis of rheumatoid arthritis (RA), being the site of evolving inflammatory reaction and autoreactive response that lead to joint destruction. Inflammatory changes within the bone marrow are seen in magnetic resonance imaging (MRI) as bone marrow edema (BME). BME was first described by Koenig et al. in 1986 [3]. It became linked to RA, as it had been found in the carpal bones of 64% of RA patients [4]. It is thought to take part in the etiopathogenesis of RA as the main source of potentially pathological cells, which migrate into the synovium or carry out their effector functions from the subchondral side (the so-called *bone-marrow – centered disease* model of RA development, in which BME is the key element) [5]. Under normal circumstances, various cells form within the bone marrow, including endothelial precursor cells (EPC), neutrophils (Nf) and dendritic cells (DC). In an active phase of RA, EPCs and DCs accumulate in the synovium, where the ectopic lymphatic tissue will form and lymphocytes will be activated in further stages of the disease. In addition, large numbers of Nfs accumulate within the joint fluid [6].

Bone marrow edema presents with increased signal in T2-weighted images, being most visible in fat saturation or IR sequences (STIR, TIRM). On the other hand, it is hypointense and less evident in T1-weighted images and becomes enhanced (hyperintense) after contrast administration [7] (Figure 1). The image of subchondral cysts/ geodes is identical to that of BME, although unlike the latter, the former are more focal lesions localized in the vicinity of bony cortex [7,8[(Figure 2). The above-described MRI picture of BME is due to a locally increased concentration of compounds containing H^+ ions, indicating that the marrow fat was substituted by water or a substance with more water and less fat content than normal bone marrow [9,10]. This is confirmed by histopathology, which shows the majority of erosions and all areas of BME to be the results of bone marrow adipose tissue substitution by inflammatory infiltrates containing macrophages, memory T cells, B cells, plasma cells and osteoclasts – a picture consistent with bone inflammation (osteitis or osteomyelitis) [10–13]. These cells may reach synovium from the bone marrow directly through bone canaliculi, or indirectly through peripheral blood after passing between the walls of the synovial blood vessels [14]. Polycellular bone marrow inflammatory infiltrates were noted near the disrupted cortex layer of the synovium (next to erosions). Based on the material obtained during arthroplasties of joints with advanced RA changes, Jimenez-Boj et al. showed that these infiltrates consisted of the pannus cells infiltrating subchondral bone, clusters of lymphocytes and numerous vessels. Similar findings were acquired in 1980 by Barrie through histopathological studies on removed metatarsal heads [15,16]. Lymphocytic infiltrate is strictly related to osteoclasts, even correlating with the number of osteoclasts as described in other studies; this association confirms the second mechanism of erosion development - from the direction of joint cavity [17,18[(Figures 3–5).

Recent publications confirmed BME to be the most significant MRI finding in RA patients, particularly those in the early phase of the disease [19]. BME appears several weeks after the onset of first symptoms and therefore, is considered a very early marker of inflammation. This is



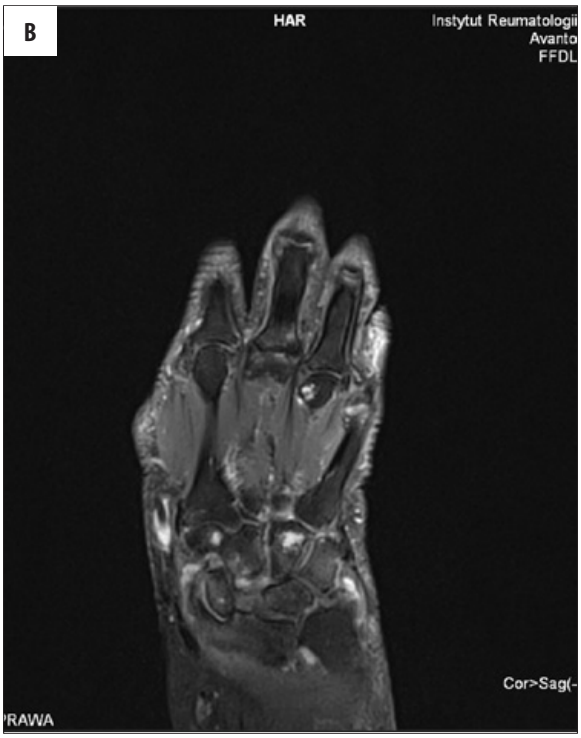


Figure 2. MRI examination, images in the frontal plane in (**A**) T1, (**B**) PD FS, (**C**) T1 FS CE image: increased signal of varied size within the endosteum and subchondrium, in the carpal and midcarpal bones.

supported by its correlation to clinical assessment of disease activity (e.g. the DAS 28 score) and to concentrations of acute-phase markers (ESR and CRP) [20]. BME is also a sensitive, but relatively non-specific parameter found in 39–75% of patients with RA lasting less than 1 year, also observed in other inflammatory diseases of joints, as well as in degenerative, post-traumatic, strain-related and neoplastic conditions [19]. In early RA, particularly affecting MSP and PIP joints, BME is located in the subchondral layer. However, it can be seen at a certain distance from the subchondral layer within carpal bones. BME may occur as an isolated finding or be located around erosions. It is reversible and can be reduced with biological treatment, e.g. anti-TNF-α drugs (18). In 50% of patients with BME, "radiological" erosions do not form as a result of early and appropriate therapy [21].

Bone marrow edema seen in MRI marks an important element of pathogenesis of RA, usually co-existing with synovitis, albeit it may be an isolated finding in some patients [5]. Sometimes inflammatory reaction may develop in the bone marrow independently of the same process taking place in the synovium, or it may precede synovitis. This data was also gathered in MRI studies [14].

Bone Marrow Edema as a Predictor of Erosions

BME is considered a "herald" of erosions [22]. The risk of forming erosions is 6-fold higher in areas where BME was noted earlier. In the time period of 6 years, BME was found to be the only parameter predicting the presence of erosions in plain radiography [15]. Other studies showed BME and male sex to be the only variables capable of predicting the risk of erosions after 1 year and 2 years [15]. Moreover, BME was twice as common in early RA patients with ACPA autoantibodies, a finding supporting its association with a rapid and aggressive course of the disease [15,18]. ACPA autoantibodies are produced by autoreactive B-cells that are able to circulate between the bone marrow, synovium and within the bloodstream. Presence of *in situ* activated T and B cells in the bone marrow of RA patients should also be emphasized [23,24]. These research findings show that

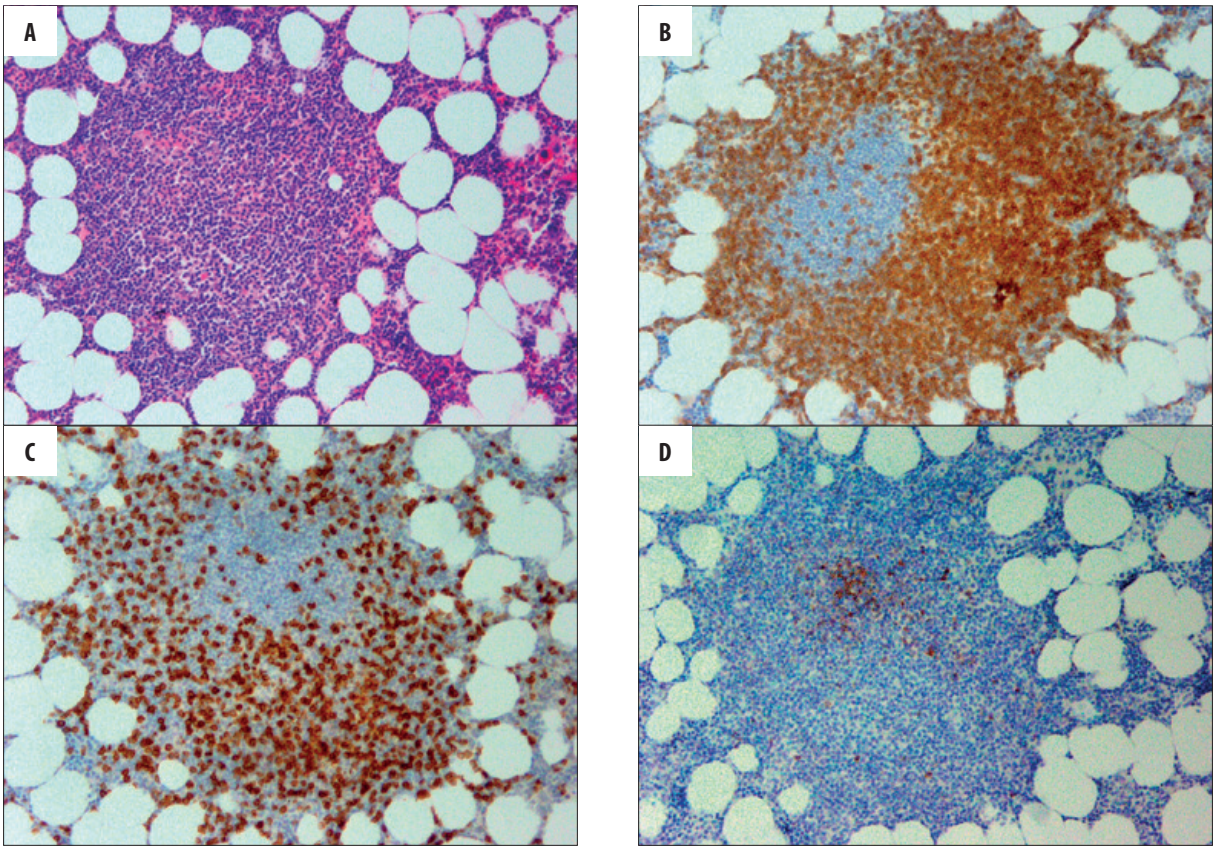


Figure 3. Histopathological picture of bone marrow obtained during endoplasty from the hip joint of a RA patient. (**A**) Numerous inflammatory infiltrates composed of lymphocytes with formation of secondary lymph follicles. Hematoxylin-eosin staining (H&E), ×200. (**B**) The majority are CD4+ Tf lymphocytes. EnVision staining, ×200. (**C**) They are accompanied by sparse CD8 suppressor T lymphocytes. EnVision staining, ×200. (**D**) Inflammatory infiltrate also contains CD23 dendritic cells. EnVision staining, ×200.

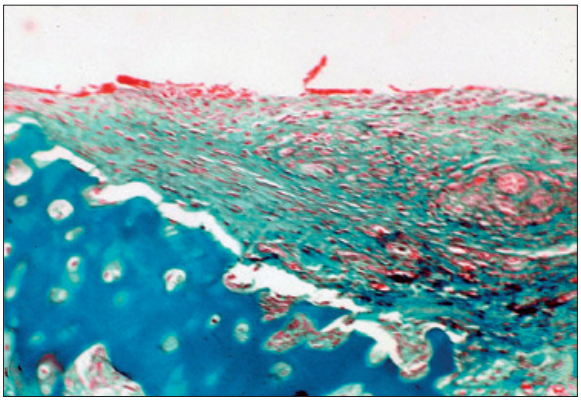


Figure 4. Pannus in a RA patient. Inflamed synovium (top) infiltrates the joint cartilage, leading to its destruction. met. Azan staining, ×200.

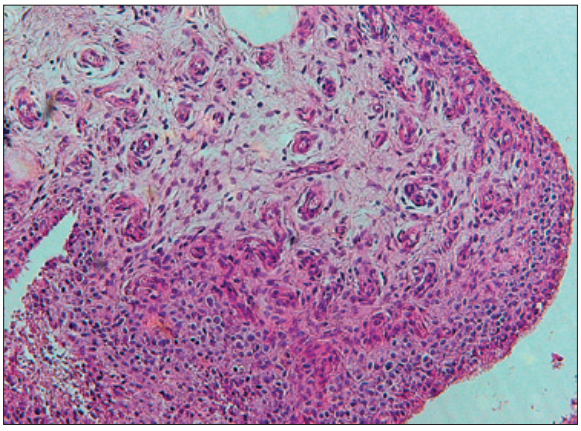


Figure 5. Angiogenesis within the synovium of a RA patient. Multiple proliferating blood vessels accompanied by inflammatory infiltrates are seen in the hyperplastic villi, H&E staining, ×200.

BME represents a fundamental aspect of RA pathophysiology and takes place in regions where active bone destruction occurs.

The relationship between BME, synovitis and development of destructive lesions in joints is not obvious. On the one hand, MRI studies confirm that synovitis is usually the primary pathology in RA and erosions only develop in joints where synovitis was, or still is, present [25]. To evidence this, the process of erosion development was hampered in the joints where inflammation of the synovium had been suppressed, [25,26]. For example, Conaghan et al. [26] demonstrated a strict correlation between an exacerbation of synovitis and the number of new erosions. These authors did not find any erosions in joints where synovitis was absent. Also, erosions were not seen until synovitis reached certain intensity, as measured in MRI (synovial thickness <1 mm in the joint that was most affected by the disease) [26]. However, other MRI and x-ray studies [25] showed

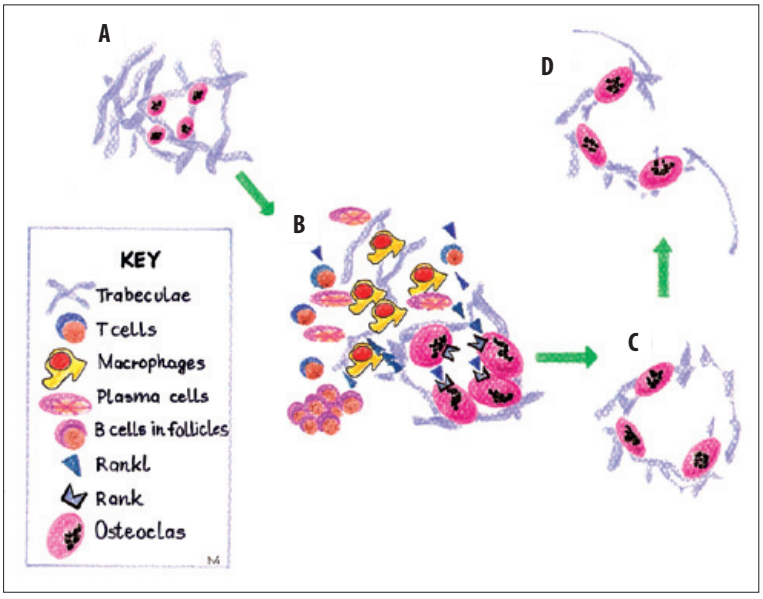


Figure 6. A model of RA with subchondral osteitis and osteoclastogenesis, in which RANKL serves as a mediator in the development of bony erosions. (**A**) a normal subchondral layer of trabecular bone; (**B**) osteitis (BME in MRI) characterized by an infiltrate consisting of macrophages, lymphocytes and plasma cells in close vicinity to osteoclasts. Multiple cells staining positive for RANKL adhere to the trabeculi; (**C**) activated osteoclasts resorbing trabecular bone, leading to the formation of an intraosseous erosion (subchondral defect visible in MRI); (**D**) results in the development of an erosion.

erosion formation in joints without clinical traits of synovitis. This finding indicates the presence of subclinical inflammation that can only be identified with MRI (BME, a small degree of synovial pathology) or USS (slight degree of synovial thickening, increased vascularity). Further supporting data come from Brown et al. [27], in whose study many RA patients in clinical and biochemical remission (according to the ACR or EULAR criteria) showed features of persistent synovitis in MRI and USS examinations. These findings predicted erosion development within one year. On the other hand, it is possible that BME is a better predictor of erosion development than synovitis [25]. It is thought that synovitis does not directly cause erosions, but rather indirectly induces them through BME. At this moment, however, these are mere speculations, although we may formulate the following series of hypotheses in a similar fashion:

1. The pannus directly leads to the development of erosions;
2. Inflammation of the bone marrow:
   a. on the one hand, causes subcortical bone destruction (this is initially seen on x-ray and USS as a geode, and later an erosion);
   b. on the other hand, inflammatory mediators and cells migrate into the joint cavity through enlarged channels within bone tissue, leading to synovitis and, in an indirect manner, to erosion formation.

In addition to this, biomechanical factors could play an essential role in the pathogenesis of erosions. As erosions have a particular tendency to form in the area of collateral ligaments of the MCP joints, they could have a common origin [25]. The volume of synovium could be twice as large at the dorsal aspect of the MCP joint compared to its lateral aspect, which predisposes to formation of erosions (the side where collateral ligaments are attached) [25].

MRI examination is more sensitive than plain radiography with regard to visualizing erosions, particularly in the carpal joints, although for a long time it was debated whether radiological erosions and those seen in MRI represented the same entities [25]. Histopathological examination of joint material obtained during arthroplasty and evaluated preoperatively with MRI demonstrated that MRI erosions correspond to bone marrow replacement by inflammatory cellular infiltrates adhering to disrupted bone cortex [10,22]. Erosions could develop as a result of cytokine release by inflammatory cells in the marrow, which stimulate osteoclast bone resorption, leading to perforation of the cortical layer and subsequent accumulation of inflammatory cells or B-cell-rich infiltrates within the synovium [10,22]. An interesting retrospective comparison of MRI and x-ray pictures of erosions showed that in 75% of cases MRI revealed a true disruption of the cortical layer (according to the RAMRIS diagnostic criteria), whereas in 25% only a focal change in the subchondrium with intact cortical layer was seen (corresponding to a geode in radiography). An early version of RAMRIS classification included such lesion in its definition of erosion, but it was withdrawn due to its low specificity. However, the above analysis proves that a focal lesion of such appearance could have a justified place in the development of erosions. This is supported by histopathological studies conducted in 2009 on samples obtained during arthroplasties. Areas where preoperative MRI had shown BME, histopathology revealed the presence of massive osteoclast infiltrates and RANKL (*receptor activator of nuclear factor kappa B ligand*) in the subchondral layer. These findings seem to capture initial bone damage taking place before continuity of the cortical layer is disrupted (Figure 6).

From a pathophysiological point of view, bone erosion and BME appear to be inherently interconnected. Bone marrow edema may subside in the course of treatment with corticosteroids, methotrexate, or biological drugs. On this basis, regression of edematous changes in the bone marrow was considered to be the evidence of erosion healing, i.e. of reversible pre-erosion inflammatory phase (Figure 6). Treatment of the erosion seen in MRI prevents formation of typical erosions visible on x-ray [25]. Clinical studies with MRI confirmed the beneficial effect of biological drugs, which decrease the number of erosions in patients

with advanced RA and prevent their appearance in early RA. In contrast, such effects were reached in only 50% of patients using of traditional treatment methods. For these reasons, it is currently debated whether methotrexate plus a biological agent should be the first-line treatment for RA patients with high risk factors for disease progression.

Conclusions

MRI is an excellent platform for conducting *in vivo* molecular studies, including those on pathogenesis of RA. For example, it was already shown that in spite of clinical suppression of synovitis, the inflammatory process leading to joint destruction in RA might persist at a histological level. Evidence for this comes from USS and MRI studies, which show thickening and increased vascularity of the synovium and/or BME despite clinical remission [25,27]. Moreover, it was shown that even a small volume of altered synovium visible on imaging studies and, even more so, BME in MRI lead to development of new erosions. However, if no signs of inflammation are found, such damage does not occur [27]. An increasing number of publications show the correlation between inflammatory changes in RA, as demonstrated in USS and MRI studies, and pathological process. Brown et al. [27] found that, among patients with clinical remission, around 50% had a picture of persistent synovitis in MRI, while a third showed such picture in USS. This also demonstrated better sensitivity of MRI. These findings could indicate that classical DMARD therapy may not suffice in bringing about complete remission. It is also possible to conclude that imaging studies should be performed in all patients to confirm clinical remission. Persistent inflammation discovered on imaging could suggest a need to modify the current treatment approach. Finally, perhaps it is a call to introduce the term "true remission" into RA, as in case of other disease entities. Such term would indicate that there were no signs of the disease in clinical, laboratory nor imaging examinations. Many questions remain, to which we still do not have answers. For example, how can we confirm remission in imaging studies if USS and MRI show individual vessels in normal joints and there is slight enhancement of the synovium after contrast injection in MRI [25]? Moreover, subclinical synovitis may occur in osteoarthritis, which quite often co-exists with RA. This all means that a certain component of synovitis may not have autoimmunological background, which is specific for RA. This is an important possibility with regard to treatment, as in patients receiving biological therapies, whose control imaging studies showed persistent synovitis. Does it have a degenerative basis? These are additional questions/challenges prompting future development of imaging studies in order to improve diagnostic specificity and further elucidate pathogenesis of the disease.

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