Histopathological evaluation and expression of the pluripotent mesenchymal stem cell-like markers CD105 and CD44 in the synovial membrane of patients with primary versus secondary hip osteoarthritis

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ABSTRACT

To present the morphological changes of classic primary versus rapidly progressive and secondary hip osteoarthritis (HO) and to examine the expression of two pluripotent mesenchymal stem cell-like markers in the synovial membrane.

A prospective observational study was conducted in 57 consecutive cases of radiologically confirmed HO in which total hip arthroplasty was performed. Based on the radiological and clinicopathological features, the cases were divided into three categories: classic primary HO (group A; n=16), rapidly destructive HO (group B; n=24), and HO secondary to avascular osteonecrosis of the femoral head (group C; n=17). Immunostains were performed using the markers CD44 and CD105. The cases from group A were mainly characterized by a marked perivascular inflammatory infiltrate and simple synovial hyperplasia. In group B, the papillary type of synovial hyperplasia was found and presence of chondromatosis, ossification, and ectopic follicles with germinal centers in the subsynovial layer was characteristic, whereas marked calcification and/or ossification were seen in group C. Focal expression of the CD105 and CD44 was noted in the hyperplastic synovial cells and subsynovial layer in cases from group A, whereas synovial cells from group B were diffusely positive for both CD44 and CD105. In secondary HO, CD44 marked the inflammatory cells. Mobilization of the CD44/CD105 positive synovial cells seems to play a role in the genesis of HO. The number of the pluripotent mesenchymal stem cell-like cells derived from the hyperplastic synovial cells might be related to the severity of possible immune-mediated rapidly destructive HO.

Significance of this study

What is already known about this subject?

- Hip osteoarthritis (HO) is diagnosed based on the radiological criteria, but the causes and steps of the rapidly destructive HO are still unknown.
- Pain intensity is not correlated with radiographic and histological changes and the mechanism of pain is still unclear.
- HO is the result of progressive degeneration of the articular cartilage and few aspects are known about the role of the synovial membrane.

What are the new findings?

- The synovial membrane is actively involved in the evolution of HO.
- Classic HO is characterized by a perivascular inflammatory infiltrate and simple synovial hyperplasia, whereas a papillary type of synovial hyperplasia and formation of germinal centers in the subsynovial layer are the main features of the rapidly destructive HO.
- The number of pluripotent mesenchymal stem cell-like CD44/CD105 positive cells derived from the hyperplastic synovial cells might be related to the severity of possible immune-mediated rapidly destructive HO.

How might these results change the focus of research or clinical practice?

- The role of the pluripotent mesenchymal stem cell-like CD44/CD105 in the pathogenesis of HO should be extensively explored.
- Intra-articular injection of immune modulators could delay the osteoarthritis evolution.

INTRODUCTION

Hip osteoarthritis (HO), also known as coxarthrosis, is the most common degenerative joint lesion in the elderly (about 50% of people aged over 65 years are affected) which morphologically steps of development are still unknown.[1 2] The primary HO is slightly more frequent in women and the favoring factors are aging, obesity, wear and tear (occupations requiring heavy lifting and elite sports activity), trauma, and ischemia.[3] The secondary HO occurs in

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patients with congenital anomalies such as hip dysplasia or avascular osteonecrosis of the femoral head (ANFH).[3] It can be also favored by calcium pyrophosphate deposition being known as the calcium pyrophosphate dihydrate crystal deposition disease (CPPD) or pseudogout.[4]

Establishing a diagnosis and determining the type of HO is usually based on the radiological assessment of the hip/pelvis, associated with the history and clinical characteristics for each patient. The radiological criteria for HO include joint space narrowing (JSN), the presence of subchondral cysts, osteosclerosis, osteophytes, and associated bone deformities.[1] The irregularly contoured radiodensities and presence of pseudotumor masses in the para-articular soft tissues are characteristic of CPPD.[4]

Pain is the major symptom of patients with HO, and because this symptom significantly decreases the quality of life it is an indication for total hip arthroplasty.[1 5 6] However, the pain intensity is not correlated with radiographic and histological changes and the mechanism of pain is still unclear.[1 5]

It is believed that HO is the result of progressive degeneration of the articular cartilage[1] and few aspects are known about the role of the synovial membrane, which refers to the synovial cells and subsynovial layer, in this disorder. This fact emphasizes the difficulties faced by health professionals in the assessment of this condition and ask for a more attentively evaluation under microscope of these cases. Lack of routine histopathological evaluation of the synovial membrane leads to an incomplete understanding of the mechanism of progressive joint deterioration in patients with HO.

In this paper, we compared the radiographic findings with the morphological features of synovial membrane in patients with primary HO versus HO secondary to ANFH. A particular aspect was also the examination of classic primary HO (secondary to acetabular dysplasia) versus rapidly destructive HO, few aspects being known about these two categories of patients. Another aspect was related to the assessment of the immunohistochemical (IHC) expression of the pluripotent mesenchymal stem cell-like markers CD105 and CD44 in the synovial membrane.

MATERIALS AND METHODS

A prospective observational study was conducted in 57 consecutive cases of radiologically confirmed HO who underwent total hip arthroplasty between June 2015 and April 2016 at the Orthopedics Clinic of the University of Medicine and Pharmacy of Tirgu-Mures, Romania. Synovial tissue was obtained at the time of hip joint replacement. The signed informed consent of each patient was preoperatively obtained and the local Ethical Committee approved the study.

Clinical and radiological assessment

On the basis of the radiological and clinical features (onset, pain duration and intensity), patients were divided into four groups: primary HO (group A; n=16), rapidly destructive HO (group B; n=24), and HO secondary to ANFH (group C; n=17).

Primary HO was diagnosed based on JSN space narrowing and the presence of osteosclerosis and large osteophytes (figure 1); rapidly destructive HO was identified by rapid clinical deterioration (in <3 years), the presence of geodes in the acetabulum and femoral head, JSN, flattening and/or partial osteolysis of the femoral head and the relative absence of osteophytes (figure 2). The diagnosis of HO secondary to ANFH was made when identifying an area of necrosis (sequestrum) and collapse of the femoral head (figure 3).

The Kellgren and Lawrence (KL) grading system was used to establish the severity of HO. The cases were categorized in four grades of severity: grade 1 (JSN and possible osteophytes), grade 2 (definite osteophytes and possible JSN), grade 3 (multiple osteophytes, definite JSN, sclerosis, and possible deformity of the femoral head), and grade 4 (large osteophytes, marked JSN, severe sclerosis, flattened epiphysis and erosions in the acetabulum).[1 7 8]

In all of the cases, joint prosthesis was performed. The aspirated synovial fluid was examined to identify pyrophosphate crystals that were also checked into the synovial membranes. No electron microscopy analysis was performed. No cases suggestive for CPPD were identified in this study.

Tissue examination

The synovial membranes were fixed in 4% neutral formalin and included in paraffin. In each case, three to four paraffin-embedded blocks were performed. Then, histologically examination using H&E stain was performed.

All of the three groups were evaluated for the integrity of the synovial cells layer and the presence of simple hyperplasia (over four layers of synovial cells) or papillary type hyperplasia (proliferation of the cells along a connective core). The presence or absence of other degenerative lesions such as necrosis, calcification, metaplastic ossification, etc was also explored. Other modifications that were checked in the subsynovial layer were the following: inflammatory infiltrate, areas of chondromatosis, calcifications, and metaplastic ossification. These modifications were quantified as minimal, focal, or well defined. All of the histological sections were independently examined by three experienced pathologists (JI, GS and TSG).

In all of the 57 cases, IHC stains were performed using the EnVision FLEX System (Dako Glostrup, Denmark) and the markers CD105 (monoclonal mouse, Novocastra, Newcastle On Tyne, UK, diluted at 1:100) and CD44 (clone DF1485, DAKO, diluted at 1:50) antibodies. For heat-induced antigen retrieval, the sections were subjected to incubation with citrate buffer (pH 6.0) for 30 min. The developing was performed with DAB solution (diaminobenzidine, Novocastra) and counterstaining was performed with Mayer's hematoxylin (Novocastra). For negative controls, incubation was performed with omission of specific antibodies.

By using CD105 and CD44 markers, we intended to identify in the synovial cells and/or subsynovial layer the pluripotent mesenchymal stem cell-like markers (MSCs), and not the assessment of microvessel density.

Statistical analysis

Statistical significance was calculated using the GraphPad Instat software (trial version) and p values <0.05 with 95% CI. The patient's age was expressed in mean±SD. For histological examination, the interobserver variability was calculated by Cohen's κ-type statistic test. The interpretation

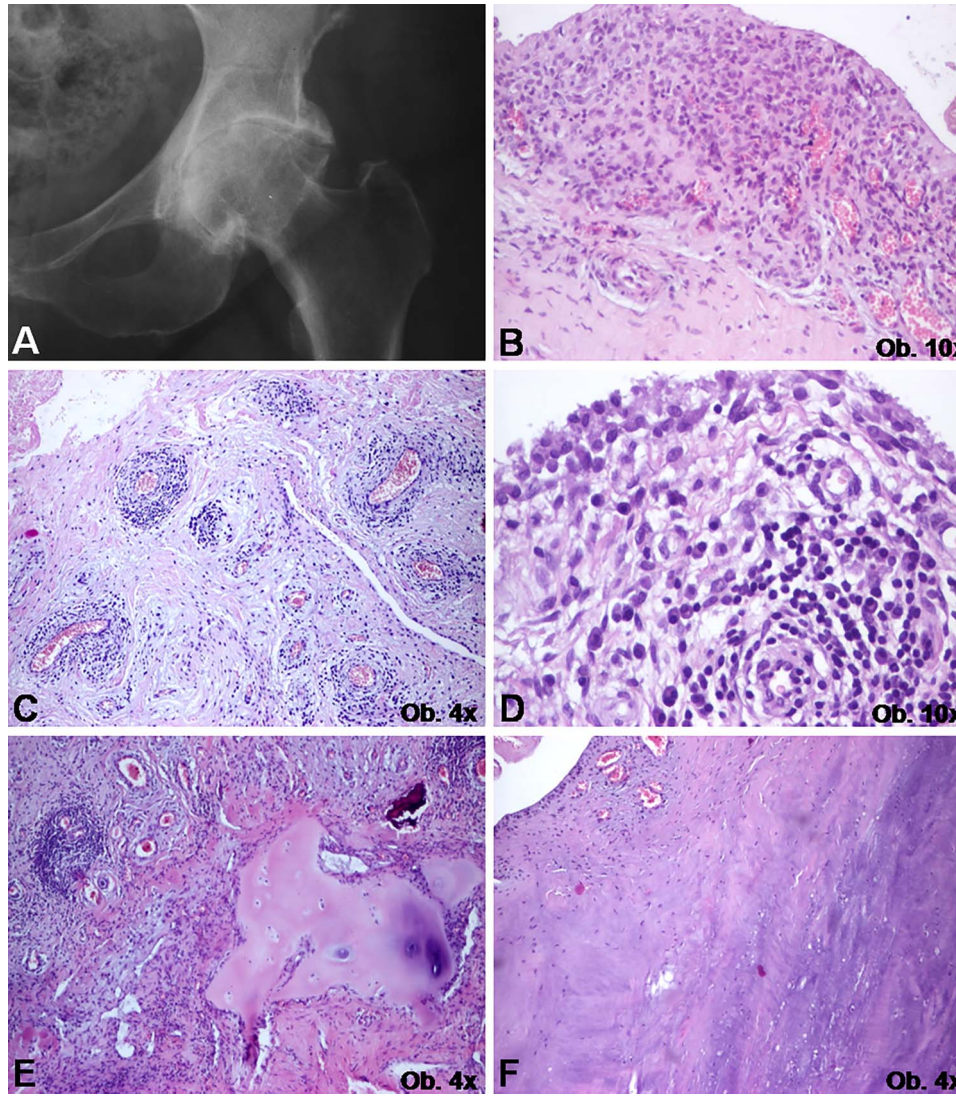

Figure 1 Primary hip osteoarthritis—(A): Anteroposterior radiographs of the hip show joint space narrowing, osteophytes, and osteosclerosis. (B–F): Histopathological features consist of simple synovial cells hyperplasia (B) and disorders of the subsynovial layer: perivascular monocytic inflammatory infiltrate (C, D), focal ossification (E), and chondromatosis (E, F).

of κ values consisted of fair (0.20–0.40), moderate (0.41–0.60), and almost perfect agreement (>0.60). In case of disagreement between the three observers, a consensus score was established for re-evaluating the cases.

RESULTS

The concordance of results between the three pathologists who examined the histological specimens was 91% and the mean κ value was 0.74. All of the cases with a fair or moderate agreement were re-evaluated.

Primary HO

From the 57 patients included in the study, 16 were diagnosed with primary HO (group A). There were 5 men and 11 women with a median age of 67.69±8.16 years (range 54 to 77 years). According to the KL classification, 6 patients had grade 3 and 10 of them showed grade 4 modifications. The femoral head was deteriorated in all cases, with macroscopic erosions of the subchondral bone of the acetabulum.

Under a microscope, the synovial cells hyperplasia was mainly simple (n=10; 62.5%), with few cases showing papillary type hyperplasia (n=6; 37.5%). The 10 cases with minimal hyperplasia displayed a well-defined perivascular inflammatory infiltrate (mainly composed by lymphocytes), large hyalinized areas, chondromatosis, and foci of subsynovial metaplastic calcification or ossification (figure 1). In the other 6 cases, minimal or no perivascular inflammation was seen and they showed papillary type hyperplasia of the synovial cells.

Regarding the IHC aspects, CD105 and CD44 were focally positive in the synovial cells and subsynovial layer (figure 4).

Rapidly destructive HO

From the 24 patients diagnosed with rapidly destructive HO (group B), 12 were men and 12 women with a median

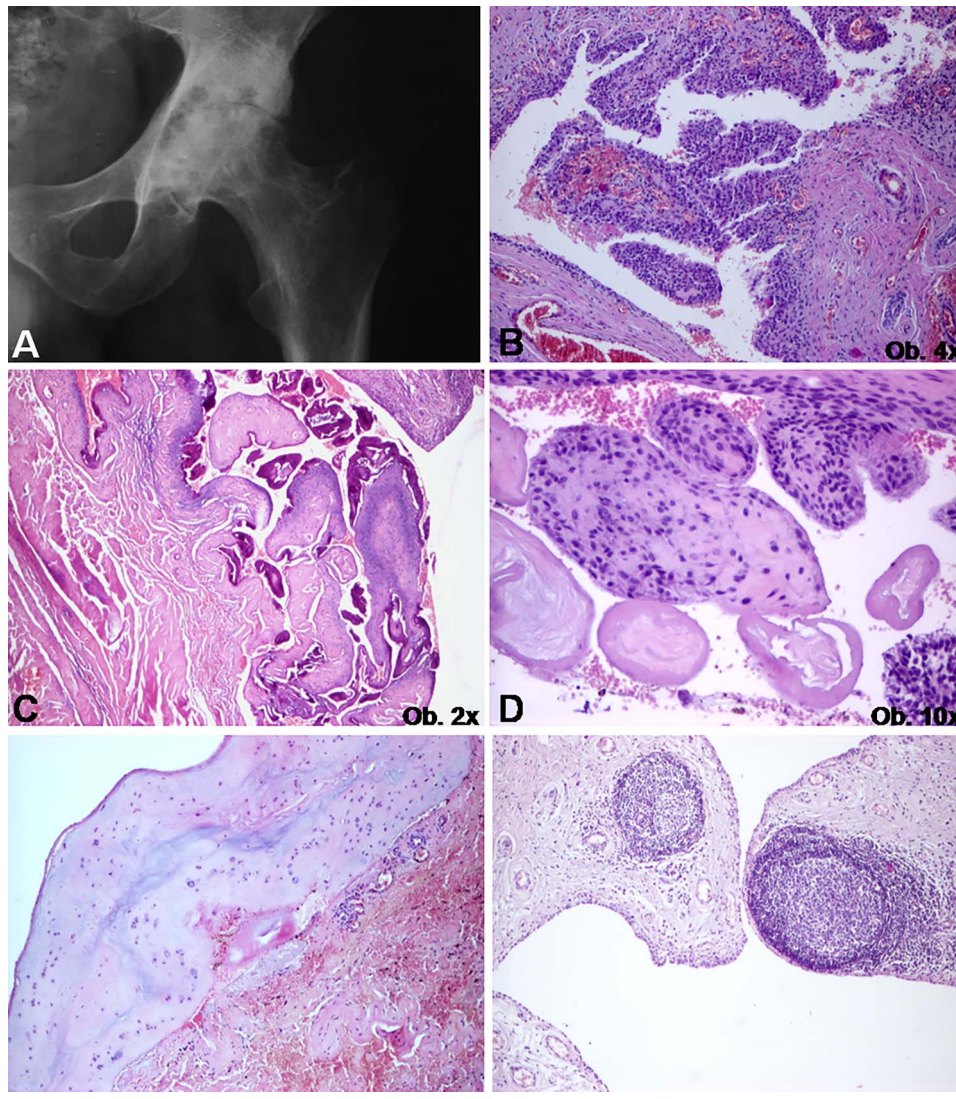

Figure 2 Rapidly destructive hip osteoarthritis—(A): Anteroposterior radiographs of the hip show joint space narrowing and geodes in the femoral head and acetabulum. (B–F): Histopathological features consist of papillary type synovial cells hyperplasia (B), with hyalinization and calcification of the papillary structures (C, D) and chondromatosis (E) and formation of follicles with germinal centers (F) in the subsynovial layer.

age of 67.42±8.51 years (range 47 to 83 years). According to the KL classification, 14 patients had grade 3 and 10 of them showed grade 4 changes.

Under a microscope, complete disintegration of articular cartilage was noted. Papillary type synovial cells hyperplasia was seen in most of the cases (n=22; 91.6%) and only two cases (8.3%) showed simple hyperplasia. In 13 of the 22 cases with papillary hyperplasia, the small papillary structures were degenerated, being transformed in free floating hyalinized or cartilaginous bodies. In all of the 22 cases, the perivascular inflammatory infiltrate was minimal or absent but follicles with germinal centers were observed in the subsynovial layer. Chondromatosis and ossification was well expressed in the subsynovial layer and among the synovial cells (figure 2). The perivascular inflammatory infiltrate was marked in the two cases with simple hyperplasia that presented disorders similar to group A.

Regarding the IHC aspects, both CD105 and CD44 were diffusely expressed in the synovial cells and subsynovial layer. CD44 also marked the ossification blades (figure 4).

HO secondary to ANFH

In group C (n=17) were 15 men and 2 women with a median age of 56.66±14.97 years (range 24–75 years). In all of the 17 cases, the morphological aspect was similar. We have noted the absence of the synovial cells hyperplasia or simple hyperplasia and marked degeneration of these cells in all of the cases, referring to hyalinization, calcification, or ossification. In the subsynovial layer, a well-defined perivascular inflammatory infiltrate and large areas of hyalinization, chondromatosis, calcification, and/or enchondral ossification were observed (figure 3).

In all of the 17 cases with secondary HO, the CD44 was expressed in the inflammatory cells and CD105 marked

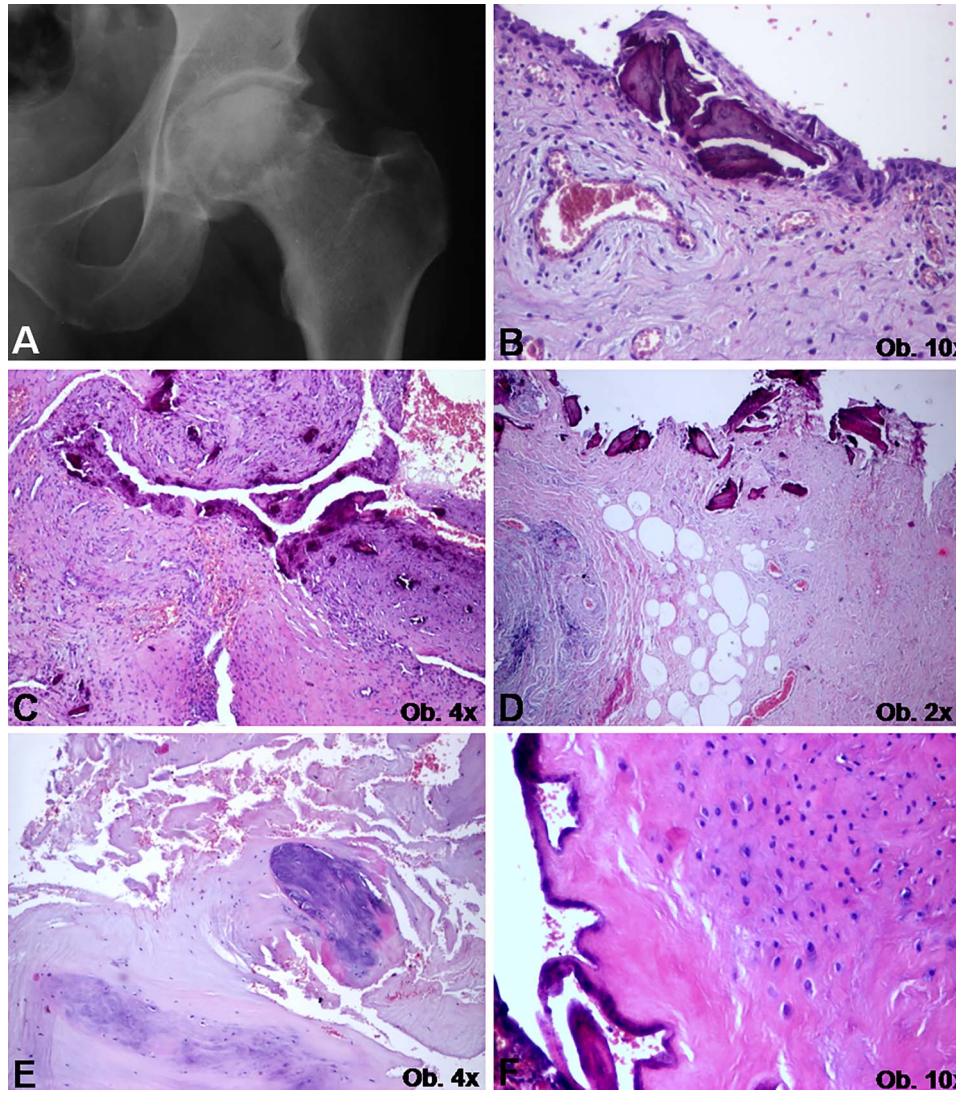

Figure 3 Hip osteoarthritis secondary to avascular osteonecrosis of the femoral head—(A): Anteroposterior radiographs of the hip show the presence of a sequestrum and collapse of the femoral head. (B–F): Histopathological features consist of hyalinization, calcification, and ossification of the synovial cells layer (B–E) and disorders of the subsynovial layer: ossification (C), perivascular inflammatory infiltrate (D), and large areas of hyalinization and chondromatosis (E, F).

few vessels and focal positivity of CD44 and CD105 was seen in the remnant synovial cells.

DISCUSSION

In HO, cartilage-related degeneration is thought to be related to on the mechanical stress and inflammatory induced biochemical changes.[1 9] The histological signs of stepwise cartilage deterioration consist of progressive loss of the cartilaginous proteoglycan matrix, chondrocytes cytoplasm enlargement followed by loss of their cellular details, increase in the chondrocyte apoptotic rate, cartilage disappearance, and its replacement by fibrotic areas.[10]

The osteoarthritis is not only a lesion of the cartilage.[9] In the subchondral areas, the necrosis, microfractures, and demineralization induce the formation of intraosseous cystic spaces, osteophytes, and osteoarticular deformities.[11] Deposition of calcium pyrophosphate within the cartilage, synovial membrane, tendons, and bursa is also supposed to contribute to the onset of HO.[12] These crystals are even 'innocent bystanders' or recruit the cytokines and maintain the inflammatory process leading to CPPD.[12–14] Their occurrence seems to be triggered by some metabolic disturbances such as hyperparathyroidism, hemochromatosis, hemosiderosis, or hypomagnesemia.[4]

In this paper, we focused on the modifications of the synovial membrane in patients with HO. It is worth mentioning that, in normal conditions, the subsynovial layer of the synovial membrane consists of a loose connective tissue rich in fibroblasts and scattered synovial cells.[15] The synovial cells layer consists of 2–3 layers of cells with a macrophage-like aspect (type A synoviocytes), which multiply during inflammatory conditions, or CD44 positive synovial fibroblasts-like cells (type B synoviocytes) having the role of producing glycosaminoglycan hyaluronic acid, a component of cartilage extracellular matrix.[16 17]

In the experimentally induced OA in rats, an edema of the synovial membrane and its infiltration with lymphocytes, macrophages, and plasma cells was noted in KL grade 1 OA, it being known that several inflammatory

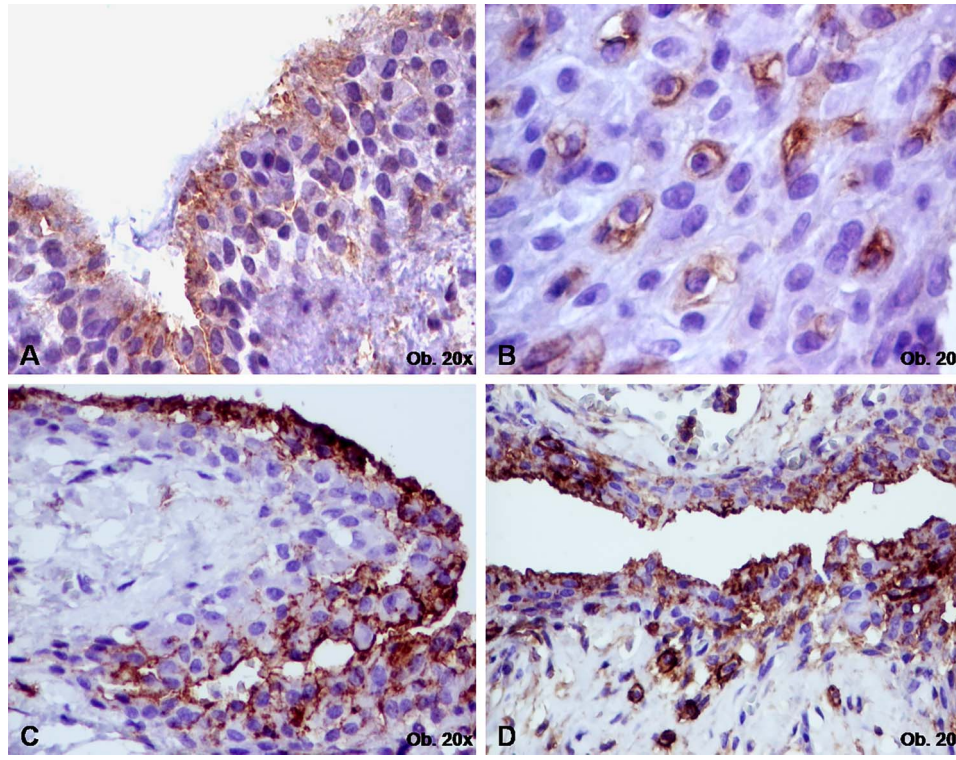

Figure 4 Immunohistochemical localization of the pluripotent mesenchymal stem cell-like markers in the hip joint. Both CD105 (A, B) and CD44 (C, D) are expressed in the synovial cells (A–D) and subsynovial layer (A, D).

markers such as tumor necrosis factor α, interleukin-6, and calcitonin gene-related peptide are upregulated in OA.[1] These changes in the synovial membrane occur before cartilage degeneration.

Our study proved that classic primary HO and HO secondary to ANFH are mainly inflammatory mediated and few CD105/CD44-positive synovial membrane-derived cells seem to mobilize. On the other hand, the severity and swift evolution of the rapidly progressive HO seems to be related to the possible immune-mediated massive mobilization of these CD44/CD105 positive synovial membrane-derived cells that display stem cell-like properties.

Similar to our findings, it was previously reported that MSCs play an important role in osteoarthritic pathogenesis, being identified in normal structures and diseased ones.[18 19] These are stromal cells which were isolated from cartilage, periosteum, synovial membrane, synovial fluid, adipose tissue, muscle, and tendons, as well as from fetal tissues, placenta, and umbilical cord.[19–22] Synovial membrane-derived MSCs can express CD44, CD73, CD90, CD105, and CD147 and rarely CD117, CD34, CD14, and CD45. They present a pluripotent ability to differentiate into osteoblasts, chondroblasts, adipocytes, and endothelial cells.[16 19 21–25] Although CD44 and CD105 positive cells are rarely seen in the healthy synovial membrane, the number of multipotent CD44+/CD90+ stem cells with high proliferative potential significantly increases in cases with experimentally induced OA in animals; the facts suggest that they can be responsible for the self-renewing cartilage.[25] The CD105 positive synovial cells are very rare and depend on the type of animal tissue that was examined.[25]

In agreement with previous studies, we revealed in cases with rapidly progressive HO (group B) papillary type hyperplasia of CD44/CD105 positive synovial membrane-derived cells and large areas of ossification between the synovial cells and in the subsynovial layer. In some of the cases, free floating intra-articular osteochondral bodies were also seen. Intensity of CD44 expression in the joint components, including the synovial membrane, is associated with the severity of changes in OA.[25 26]

Overexpression of the MSCs markers in the synovial membrane might indicate the increased migration capacity of CD44 positive fibroblast-like synovial cells but also implies the possibility to use them with potential therapeutic benefit for cartilage regeneration[19 27 28] in primary HO. However, in rapidly destructive HO, total arthroplasty remains the therapy of choice, as the cartilage is already deteriorated and papillary type hyperplasia with degenerative disorders predominates. Intra-articular injection of immune modulators could delay the OA evolution in these patients.

In conclusion, primary HO seems to be characterized by simple synovial cells hyperplasia and inflammatory mediated mobilization of CD44/CD105 positive synovium-derived MSCs. The severity of rapidly destructive HO might be related to immune-mediated mobilization of CD44/CD105 positive synovial membrane-derived MSCs.

The negative facts of the study are the small number of examined cases and absence of patients with CPPD. This negative finding might be done to absence of examination using the electron microscope. Our hypothesis should be tested in further researches on CPPD cases and the synovium should be more attentively examined to exclude the CPPD.

Contributors SGT performed the interpretation of the histological stains and drafted the article. IJ performed the interpretation of the histological stains, the immunostains and examined the synovial fluid smears. SG designed the research and the paper structure and approved the final variant. AZ analyzed literature data regarding radiological aspects of osteoarthritis. AF performed the histological daily diagnosis and checked the English quality. COR participated in the surgical interventions and managed the clinical data. MT performed the interpretation of the literature data regarding the immunostains. TSP performed the surgical interventions, managed the clinical data and approved the final variant.

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Competing interests None declared.

Patient consent Obtained.

Ethics approval Clinical County Hospital of Tirgu-Mures, Romania.

Provenance and peer review Not commissioned; externally peer reviewed.

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