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PROCEEDINGS OF THE LATVIAN ACADEMY OF SCIENCES. Section B,
Vol. 73 (2019), No. 4 (721), pp. 317–324.

DOI: 10.2478/prolas-2019-0050

SYNOVITIS IN OSTEOARTHRITIC PATIENTS: MORPHOLOGICAL AND VIROLOGICAL EVIDENCE OF ITS CONTRIBUTION TO DEVELOPMENT OF THE DISEASE

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The role of inflammation in the development of osteoarthritic joint degeneration is not completely understood. Recent data suggest that processes that cause and orchestrate inflamed synovial lesions may be implicated in the development of the disease. The morphological changes of the synovium in patients with osteoarthritis (OA), as well as the level of synovial inflammation cautiously graded, in association to the presence of human parvovirus B19 (B19V) infection markers, were evaluated. Qualitative and quantitative detection of B19V genomic sequence was performed in OA and rheumatoid arthritis (RA) groups. The expression of CD68, S100 (Ca^{2+} binding proteins soluble in 100% ammonium sulfate) and B19 VP1/VP2 capsid proteins found in the synovium were investigated by single and double immunolabeling, whereas fine features of synoviocytes — by electron microscopy. One-third of OA and RA patients demonstrated synovial expression of B19V antigen, which was confirmed in both types of synoviocytes. The overall expression of B19V in OA patients was weaker than that found in RA subjects. Positive correlation between B19V-positive vascular endothelial cells, sublining infiltrating lymphocytes, macrophages, and B19V-positive synoviocytes was established. No correlation between synovitis score indices as well as the expression of S100 and expression of B19V was found. The results suggest that the synovial membrane maintains local joint homeostasis, and that virus mediated synovitis is implicated in the development of OA.

Key words: *osteoarthritis, synovium, human parvovirus B19 infection, morphology.*

INTRODUCTION

Osteoarthritis (OA) is a common multifactorial, chronic and progressive joint disease that affects millions of people globally and has a significant economic impact on welfare (Arden *et al*., 2013; Vila, 2017). OA causes pain in the affected joint followed by loss of range of motion and joint destruction. The changes in OA include cartilage breakdown, the formation of osteophytes, extracellular matrix degradation, and destabilisation of subchondral bone synthesis with the development of subchondral sclerosis and cysts. OA has a variable course when exacerbations follow relative tranquil periods. Two major types of OA are widely recognised: primary and secondary, or symptomatic and radiographic, accordingly. Despite the sufficient body of evidence gained on OA, our understanding is far from complete. Previously, the aforementioned features were interpreted as the most common changes found in OA, but more recently a role of inflammation in the development of joint destruction has been highlighted. Furthermore, a growing pool of evidence suggests that synovitis (Mainil-Varlet *et al*., 2003; Benito *et al*., 2005; Wenham *et al*., 2010) is the prominent etiopathogenic factor in the development of OA. More recently, Atukorala *et al*. (2016) suggested that synovitis is a precursor of radiographically evident OA, and treating synovitis in OA may have a role in reducing progression of the disease. Conventional radiography methods are unable to visualise the inflamed and thickened synovial

membrane, whereas use of ultrasonography method has not yet been verified in large-scale studies of OA (Hayashi *et al*., 2011). Therefore, an advanced search for higher efficacy of the synovitis evaluation continues to grow.

The synovial membrane presented by its intimal and subintimal layers constitutes the innermost part of the joint envelope. The intimal layer, in turn, contains two cell types — fibroblast-like (FLS) and macrophage-like synoviocytes (MLS). In osteoarthritis patients, various synovial inflammatory cells and pro-inflammatory agents contribute to sustained joint destruction (de Lange-Brokaar *et al*., 2012). Elevated levels of interleukine (IL)-1β, tumour necrosis factor alpha (TNF-α), IL-6, IL-7, vascular endothelial growth factor (VEGF) and numerous other cytokines have been found in sera, synovial fluid, and synovium of OA patients (Vila, 2017). The innate immune system including its cellular and humoral defence mechanisms has a significant impact on the synovium structure and function (Xia *et al*., 2018). Furthermore, various immune system cells producing S100 Ca^{2+}-binding proteins found in high amounts in the synovial fluid in the case of OA are believed to promote further degradation of tissue, eliciting a catabolic effect in human osteoarthritic chondrocytes (Cecil *et al*., 2005; Schelbergen *et al*., 2012). However, CD68, which is commonly used as an inflammation marker recognising lysosomal proteins is believed to play a crucial role in the development OA and sustaining chronic inflammation (Claire *et al.,* 1993; Manferdini *et al.,* 2016). Despite prolonged studies, the aetiology of OA exacerbations and inflammation drivers remains unknown. However, one of the possible candidates contributing to the pathogenesis of OA could be a viral infection, which has been implicated in other inflammatory arthritides, like rheumatoid arthritis. Furthermore, it remains controversial whether human erythrovirus strains related to human parvovirus B19 provoke OA or worsen the clinical presentation of the disease (Aslan *et al*., 2008).

B19V is a widespread virus infecting various cellular types (Cooling *et al*., 1995; Söderlund-Venermo *et al*., 2002; Adamson-Small *et al*., 2014). Synovial membrane and joints have been mentioned among the most common B19V affected tissues in adults (Mauermann *et al*., 2016), but the presence of parvovirus B19 DNA in synovial tissue of patients with joint inflammation does not allow the diagnosis of parvovirus-induced arthritis (Schmid *et al*., 2007). The B, T lymphocytes and antigen-presenting cells (macrophages and follicular dendritic cells (DC)) have been recognised as cellular targets and considered to be productively infected by B19V in affected joints (Takahashi *et al*., 1998; Lennerz *et al*., 2004; Chen *et al*., 2006). Further demonstration of the resistance of globoside-negative individuals to infection with B19V explained the role of this receptor in the infectious process as well as co-receptors in virus binding and internalisation (Gallinella, 2013). Simultaneously, the interplay between the pathogenetic potential of the virus and tissue constituents has been defined as a significant predictor of outcomes of B19V infection, but unfortunately, is far from a comprehensive understanding (Kerr, 2000; Stoppiello *et al*., 2014). Very few studies related to the phenotypic changes of synoviocytes inducing an invasive phenotype in FLS and facilitating cellular migration have been performed in the case of B19V infection (Ray *et al*., 2001; Lu *et al*., 2006).

The present study aimed at investigating the synovium changes in osteoarthritis subjects by means of morphology and virology methods. Also, the Krenn and Morawietz score, which better reflects the grade of synovitis and increases reproducibility of histopathological data, was evaluated and statistically analysed.

MATERIALS AND METHODS

Patients and controls. OA patients were recruited from Rīga East University Hospital Clinic "Gaiļezers". Subjects who underwent a joint replacement surgery for OA between January 2016 and September 2018 were enrolled in the study. The study protocol and the use of the synovial membrane samples were approved by the Ethics Committee of Rīga Stradiņš University (Decisions of 27.05.2014 and No. 2/08.09.2018), and a written informed consent was obtained from all patients. The inclusion criteria were primary or previously established diagnosis of OA established in the given hospital. All OA subjects fulfilled relevant American College of Rheumatology (ACR) criteria for the disease affected joints: hip (Altman *et al*., 1991) and knee (Altman *et al*., 1986).

Fifty-four subjects enrolled in the study (mean age 65, range 35–85 years, standard deviation (SD) 12.27 years; 19 males and 35 females) had OA confirmed clinically and radiologically and did not reveal any objective and subjective evidences of any other inflammatory disease apart from OA. Seven subjects with rheumatoid arthritis as a primary joint disease (mean age 65, range 35–67 years, SD 9.1 years; one male and six females) constituted a comparison group.

Molecular virology. Initially, the subjects were screened for B19V-related IgG and IgM antibodies. The synovial tissue total DNA was obtained using standard phenol-chloroform extraction. Concentration of extracted DNA was measured spectrophotometrically (Nanodrop ND-1000 Spectrophotometer, Thermo Fisher Scientific, Waltham, MA, USA) and the quality of DNA tested by detecting the presence of the β-globin gene sequence using polymerase chain reaction (PCR) (Naciute *et al*., 2016) (C1000 Touch Thermal Cycler, Biorad, Hercules, CA, USA).

For quantitative detection of B19V genomic sequence real-time PCR (qPCR) was performed in both the OA and RA groups. A commercially available qPCR kit (B19V Real–TM Quant, Sacace Biotechnologies Srl, Italy), which included the standards, the positive and the negative controls, was used to detect the B19V VP1 genomic region.

Estimation of synovitis using Krenn score. To better grade synovitis and obtain reproducible histopathological data, the Krenn and Morawietz score was used (Krenn *et al*., 2006). Cellular hyperplasia of intimal layer, cellular density of subintimal layer and inflammatory infiltration were semiquantitatively estimated: 0 – absent, 1 – mild, 2 – moderate, and 3 – strong. Additionally, we estimated the presence and density of congested synovial capillaries scored in the subintimal layer as follows: 0 – few, 1 – small numbers of profiles, which are loosely packed, 2 – moderate numbers, which are more densely packed, and 3 – high numbers of profiles revealing dense spatial distribution. The sum obtained provided the synovitis score, which was interpreted as follows: 0–1, no synovitis; 2–4, low-grade synovitis; and 5–9, high-grade synovitis.

Immunohistochemistry. Immunohistochemistry (IHC) either as single or double immunolabelling was performed manually using sections collected on SuperFrost Plus slides (Gerhard Menzel GmbH, Germany). For single antigen detection, sections were deparaffinised, and endogenous peroxidase activity was blocked with 0.1% H_2O_2 in methanol. Heat-induced antigen retrieval was accomplished with the sections placed in 10 mmol/l sodium citrate buffer pH 6.0 for 30 min in a vapour lock. Non-specific binding was blocked with 1% bovine serum albumin/5% normal goat serum in phosphate buffered saline. Immunohistochemistry was performed manually using incubation at 4 °C overnight with the following primary antibodies: monoclonal anti-B19V antibody reacting with B19 VP1/VP2 capsid proteins (Novocastra, Leica Biosystems, Newcastle, UK, clone R92F6, 1 : 20); and monoclonal mouse anti-human S100 (Cell Marque, Rocklin, CA, USA, clone 4C4.9, 1 : 100). Amplification of primary antibody and visualisation of reaction products was performed applying the HiDef Detection Horseradish Peroxidase (HRP) Polymer system (Cell-Marque, Rocklin, CA, USA) or Novolink Plymer Detection System and diaminobenzidine tetrahydrochloride (DAB) substrate kit (UltraMarque HRP Detection system). Finally, the sections were washed with distilled water, and counterstained with Mayer's hematoxylin.

For double labelling confirming the presence of nuclear B19V and cytoplasmic CD68 localisation, simultaneously the EnVision™ Gl2 Doublestain kit (DakoCytomation, Glostrup, Denmark 1 : 50) was used. Sections were incubated for 5 min with Dual Endogenous Enzyme Block, buffer washed, incubated with anti-B19V antibody for 10 min, Polymer/HRP, and DAB+ Working Solution for up to one hour at room temperature 20–25 °C, rinsed; then incubated with Doublestain Block, thereafter with anti-CD68 antibody for 10 min, Rabbit/Mouse LINK, rinsed, incubated with Polymer/AP for 10 min, rinsed, and incubated with Permanent Red Working Solution for 20 minutes. Then the slides were rinsed in a fresh distilled water for five minutes, counterstained with Mayer's hematoxylin, washed with water, mounted, and covered with coverslips. Cells that were labelled with the above-mentioned antibodies and displayed brown (both brown and red for doublestaining) reaction products were considered immunopositive. Sections from cases with known antibody positivity were used as positive controls. IHC controls that included substitution of the primary antibodies with tris(hydroxymethyl)aminomethane (TRIS) solution (pH = 7.4) were used as negative controls. The sections were photographed under a Leitz DMRB microscope using a digital camera DC 300F.

For immunofluorescence, sections were counterstained with 4',6-diamidino-2-phenylindole (DAPI) (Thermo Fisher Scientific, Invitrogen, UK, 1 : 3000) and embedded in Prolong Gold with DAPI (Thermo Fisher Scientific, Invitrogen, UK). Tissue autofluorescence was suppressed by 0.2% Sudan Black B solution (Sigma Aldrich, St. Louis, MO) before cover slipping. The sections were examined with a Leitz DMRB (Leitz, Germany) using a digital camera DC 300F and Nikon confocal microscope Eclipse Ti-E (Nikon, Japan).

Electron microscopy. Synovial tissue samples were fixed in 2.5% glutaraldehyde in 0.1 M phosphate buffer at pH 7.4, postfixed in 1% OsO4, dehydrated in a series of graded ethanols and acetone, and embedded in epoxy resin. Ultrathin 60-nm-thick fine sections were cut with an LKB ultramicrotome, collected on copper grids, double stained with uranyl acetate and lead citrate, and examined with a JEOL 1011 transmission electron microscope (JEOL JEM 1011, Japan) at accelerating voltage 80–100 kV and at magnification 4000–30 000×.

Statistical data analysis. Statistical data analysis was performed in order to estimate the immunohistochemistry results. A Kolmogorov-Smirnov normality test was used to detect any differences between samples. The quantitative data were expressed as means ± standard deviation and as medians with interquartile range (IQR), whereas categorical parameters were expressed as frequencies and percentages. Two values were considered to be statistically significantly different in cases when the confidence level of the difference between them was greater than 95% ($p < 0.05$). The SPSS version 24.0 software was used for statistical analysis.

RESULTS

Polymerase chain reaction. In the arthritic subjects, the B19V VP1 genomic sequence was detected in 6 of 58 (10.3%) synovial membrane tissue samples, in 3 out of 51 (5.8%) OA and in 3 out of 7 (42.9%) RA patients, respectively. Furthermore, the B19V VP1 genomic sequence was identified in a RA case with high-grade synovitis.

Conventional light microscopy. Conventional light microscopy of the OA lesioned synovium samples demonstrated hyperplasia of synovial lining, sublining fibrosis, and stromal vascularisation (Fig. 1A). Macrophage and lymphocyte infiltration in the synovium was common as well (Fig. 1B). Some macrophages were clustered and formed multinucleated giant cells. A Kolmogorov-Smirnov test was performed on all statistical data. The test revealed

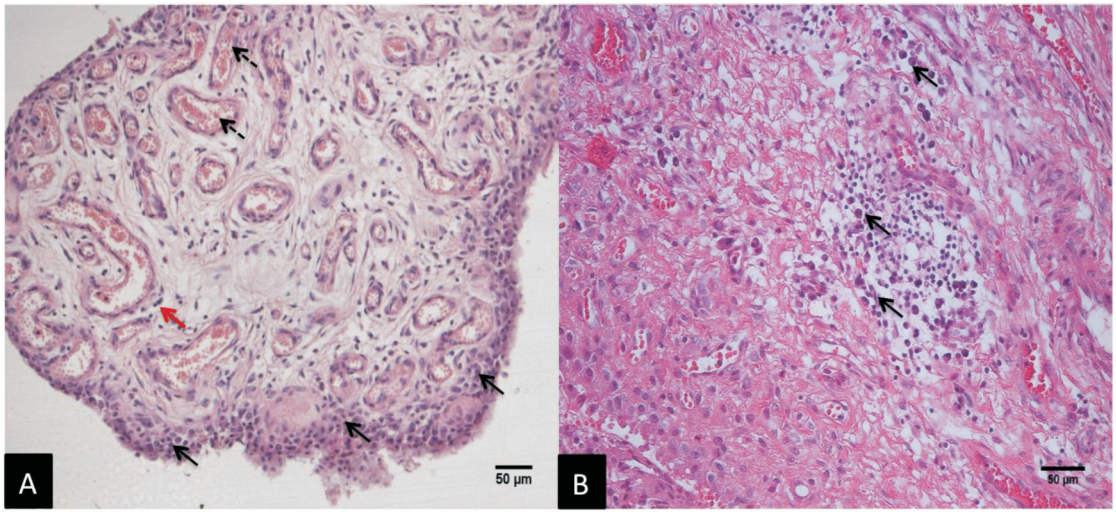

Fig. 1. Histopathology of the OA lesioned synovium. (A) Synovium with hyperplasia of the lining layer (black arrows) showing congested capillaries (black dashed arrows), and occasional inflammatory cells (red arrow), ×200. (B) The synovial area in a case of chronic synovitis is manifested with the lining hyperplasia and lymphoid and plasma cell infiltration (black arrows), ×200.

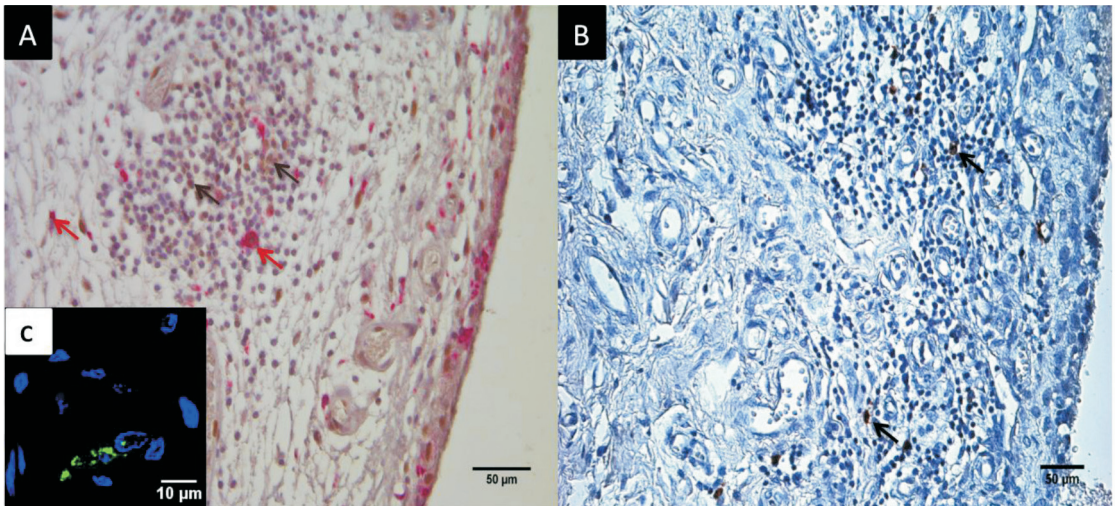

Fig. 2. (A) Double immunohistochemical staining using two monoclonal antibodies targeting CD68 (red arrow) and B19V (brown arrow) in the synovium of OA subject. Image depicts lysosomal proteins within synovial macrophages (red arrow) and nuclei of vascular endothelial cells, FLS and some macrophages stained for B19V (brown arrow), ×400. (B) S100 synovial immunoreactivity revealed mostly perivasculary (black arrows), ×250. Insert (C): immunofluorescence demonstrating nuclei of synoviocytes and sublining stroma cells stained with DAPI (blue) and VP1/VP2 capsid proteins (green).

that the Krenn score did not follow a normal distribution (D44 = 0.176, $p = 0.002$), and the blood vessel index did not follow a normal distribution (D43 = 0.218, $p < 0.005$). Congested synovial capillaries presented with the median value 1.0 IQR (2.0).

Estimation of synovitis using the Krenn score revealed great range — from 0 up to 5 with median value 2.0, IQR (2.0). Low-grade synovitis was found in the majority of cases (10 out of 44 (22.72%). 5 (11.36%). OA subjects revealed the absence of synovial inflammation, whereas 4 (9.75%) presented with moderate synovitis.

Immunohistochemistry. Eleven of 39 (28.2%) OA and two of 7 (28.6%) RA subjects showed positive synovial staining of B19V antigen. Double labelling using anti-B19V and anti-CD68 antibodies showed expression of viral proteins in both synovial cellular types — macrophages and FLS (Fig. 2A and insert C). The overall expression of B19V in OA patients was either weak or mild, but one patient demonstrated a strong decoration of the synovium with the anti-B19V antibody. Virological analysis of this patient confirmed acute viremia. Also, positive B19V expression was strong in red bone marrow cells, mostly erythroid and blood platelet cell lines, vascular endothelium and muscular cells. Furthermore, a positive correlation between B19V-positive vascular endothelial cells and erythroid cells in the red bone marrow (r = 0.846, $p < 0.004$), and between B19V-positive vascular endothelial cells and B19V-positive synoviocytes (r = 0.579, $p = 0.001$) was found. In contrast, no correlation between synovitis score indices reflecting synovial inflammation and expression of B19V was found. Mild to strong synovial expression of B19V was demonstrated in RA patients. A strong positive correlation (r = 0.744, $p < 0.001$) and r = 0.696, $p < 0.0001$) was established in the synovium of OA subjects when B19V-positive synoviocytes and sub-

lining infiltrating lymphocytes and macrophages were estimated, respectively (Fig. 3A and 3B).

Unequal synovial expression of S100 family proteins was noticed in the samples studied — S100 positivity was found in 14 patients of 61 (23%). The expression was mostly moderate, and anti-S100 decoration displayed both diffuse and local distribution pattern. The synovial lining macrophages and follicular dendritic cells displayed S100 expression (Fig. 2B). No statistically significant correlation between synovial expression of parvovirus B19 viral proteins and expression of S100 was found.

Transmission electron microscopy. Transmission electron microscopy examination of the lining layer demonstrated irregularly shaped cells revealing a large number of extensions of the cell membrane (Fig. 4A). The plasma membrane of MLS possessed numerous fine extensions characteristic of macrophages. The cytoplasm of MLS revealed conspicuous cisternae of Golgi apparatus, phagosomes, large vacuoles, and small vesicles localised around the nucleus. FLS revealed prominent cytoplasmic extensions that often extended into the surface of the synovial lining. Invaginations along the plasma membrane were frequent. FLS displayed mostly a phenotype evidencing extensive synthetic activity — abundant rough endoplasmic reticulum and the Golgi apparatus; polymerised, greatly varying collagen microfibrils occurred nearby (Fig. 4.B). Inflammatory cells (occasional lymphocytes, clustered lymphocytes, and plasma cells) were observed in the case of synovitis.

DISCUSSION

Osteoarthritis is a common joint disease affecting the entire joint and particularly soft tissues. Usually, the disease manifests in OA patients in their sixties. However, undisputed evidence suggesting that OA may develop in younger people was provided, thus highlighting contribution of other factors than mechanical wear to the disease (Sulzbacher, 2012). Investigation of the synovitis in OA damage has re-

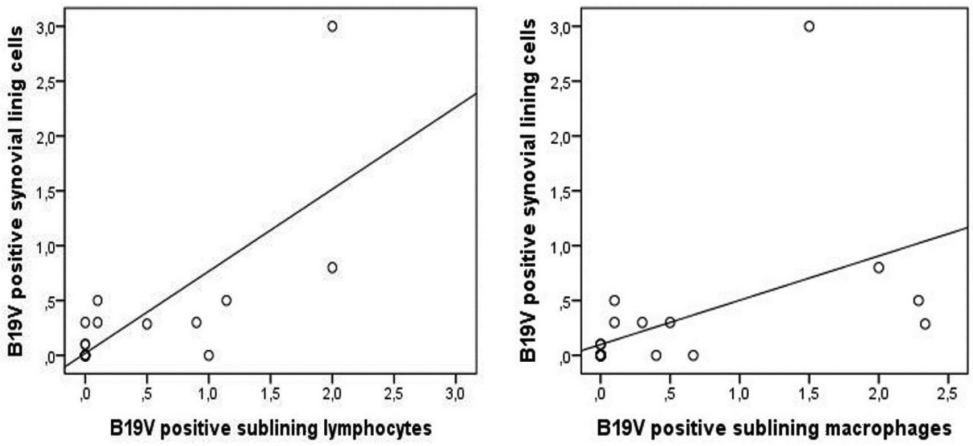

Fig. 3. (A) Correlation between B19V-positive synoviocytes and sublining infiltrating lymphocytes. (B) Correlation between B19V-positive synoviocytes and sublining macrophages.

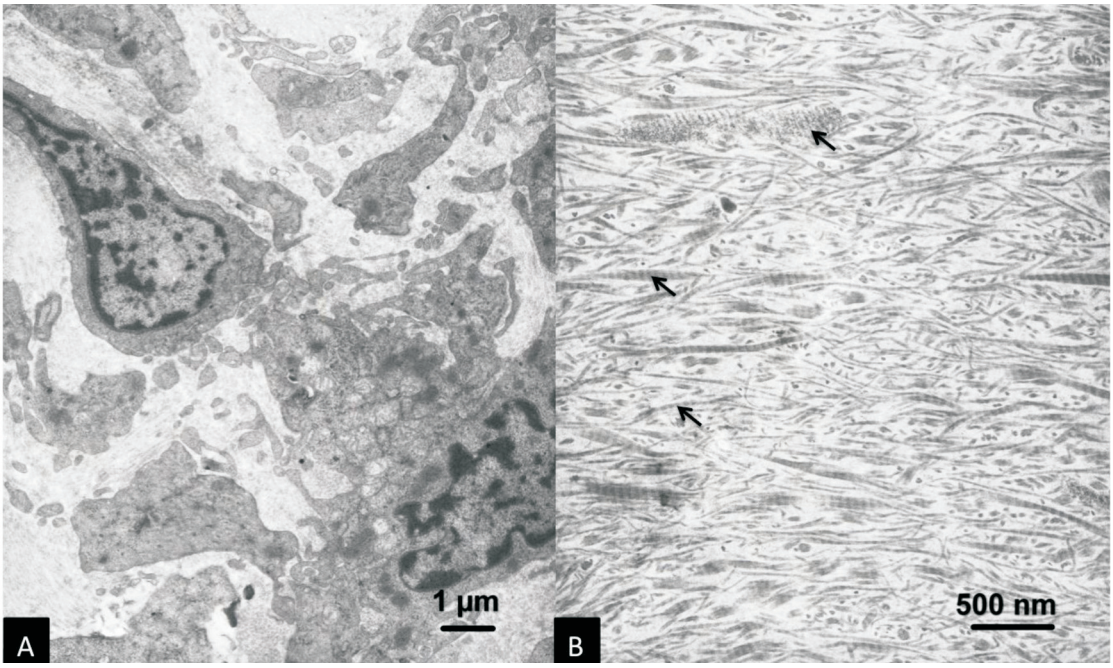

Fig. 4. Synovial membranes pathological histology findings on transmission electron microscopy. (A) Fine structure of the synoviocytes revealed using transmission electron microscopy, ×10 000. (B) Great variation in both by fine structure and diameter of collagen microfibrils (black arrows) revealed using transmission electron microscopy within the sublining layer, ×15 000.

ceived much attention of the scientific community during the last decade (Sellam *et al*., 2010; Mathiessen *et al*., 2017). Furthermore, viruses were recognised among inflammation inducers and factors contributing to OA relapsing nature (Rollín *et al*., 2007). Previous studies have demonstrated that B19V, hepatitis B and C as well as HIV are among the most common causal agents of virus-mediated arthritis worldwide (Marks *et al*., 2016). Furthermore, despite the fact that most virus-mediated arthritides are self-limiting, these often require careful consideration of virological, clinical, laboratory and other features to guide physicians in making diagnostic and treatment decisions. B19V DNA prevalence in synovial tissue of RA patients has been shown in several studies, including cohort studies investigating the presence of B19V infection markers (genomic sequences and virus-specific antibodies) in association with the level of cytokines and RA clinical activity and aggressiveness (Naciute *et al*., 2016). Very few studies have been reporting on the influence of B19V in OA patients (Rollín *et al*., 2007; Aslan *et al*., 2008). Difficulties arising around the excellent diagnosis of parvovirus-induced arthritis have been reported previously (Schmid *et al*., 2007), even in cases confirmed by the presence of parvovirus B19V DNA in synovial tissue. Our results show that 16 of 54 (29.6%) OA patients are infected with B19V; none of them had an exacerbation of the disease. One of the subjects enrolled in the study presented with viremia and a high number of infected synovial cells confirmed immunohistochemically. The presence of B19V infection markers was detected in both OA and RA groups of patients, and was more heavily expressed in RA subjects (42.9%), thus highlighting the necessity of further studies addressed to larger cohorts of Latvian population. Sensitivity and specificity of PCR and IHC data is a commonly debatable issue. Molecular virology methods are sufficiently used when quick screening and diagnostics is requested, whereas IHC labelling is used to access more information on the number and cell types contributing to either degenerative or inflammatory process characteristic of the arthritic lesion.

In contrast, the level of C-reactive protein (CRP) was only slightly elevated, and the Krenn score index was low. In this context, the results are in accordance with previously reported data suggesting the persistence of B19V in subjects without clinically evident complains characteristic of arthritis (Söderlund *et al*., 1997; Watanabe *et al*., 2018). Furthermore, B19V-related arthralgia is usually self-limited but may persist for several months or recur over months to years (Bultmann *et al*., 2003; von Landenberg *et al*., 2007).

According to the proposal made by Gallinella (2013), outcomes of B19V infection depend on the interaction between the pathogenetic potential of the virus, its adaptation to different cellular environments, and the physiological and immune status of the infected individuals. To better understand the contribution of synovial inflammation in general, and changes of synoviocytes in particular, to the clinical manifestations of OA and exacerbations of the disease, we have performed immunohistochemistry and electron microscopy investigations. The results of double staining immunohistochemistry suggest B19V persistence and demonstrate that the B19V sequence is present in both types of synoviocytes — FLS and MLS. Furthermore, it has been generally considered that FLS bear cytological characteristics of the nonpermissive cells, which are not able to sustain the viral replication. Simultaneously, the significance of the differentiation stage and physiological state of cells essential for the virus to complete a productive cycle has been highlighted in recent investigations (Gallinella, 2017). Our immunohistochemistry results demonstrate that viral capsid proteins are found in the synovium of OA patients, and more specifically — FLS. This is consistent with previous results (Magro *et al*., 2004), which show the presence of B19V in the skin fibroblasts of scleroderma patients followed by the unregulated release of TNF-α. Furthermore, B19V NS-1 protein activates proinflammatory growth factor – TNF-α and IL-6 encoding genes (Fu Y *et al*., 2002; Mitchell *et al*., 2002). FLS in the heavily populating intimal layer may either develop from migratory cells bearing precursor features or arrive from the circulation or residential cell pool located in the synovium and bone (Tolboom *et al*., 2002; Mor *et al*., 2005; Steenvoorden *et al*., 2007). Viral exposure may cause the phenotypic changes and aggressiveness of FLS accompanied by increased production of matrix metalloproteinases (MMP) and other extracellular matrix degrading molecules further contributing to joint destruction (Bartok *et al*., 2011). Furthermore, activity of IL-6, IL-1β mRNA and matrix metalloproteinase 9 (MMP9) increases in cells treated with B19 VP1 protein (Tzang *et al*., 2009). The presence of other receptors (as exemplified by studies with erythropoetin receptor) and co-receptors of globoside seems to be essential for B19V to complete the replication cycle (Chen *et al*., 2010). Pathogenic pathways of B19V-associated with autoimmunity include cross-reaction of anti-B19V antibodies with human proteins and B19V-induced apoptosis, which results in presentation of self-antigens to T lymphocytes, and the VP1 region-related phospholipase activity (Kerr *et al.,* 2016). This, at least partly, explains a broad spectrum of cells and tissues infected by B19V (Gallinella, 2017; Munakata *et al*., 2018), but intimate details of the synovial cellular affection in case of OA are far from being complete, and similarities of B19V exposure in RA and OA patients cannot be excluded (Naciute *et al.,* 2017).

Ca^{2+}-binding protein S100 was found in abundance in rheumatic disease, stimulating inflammatory cell motility and cytokine release (Donato *et al*., 2013). Nakashima *et al.* (2012) showed elevation of S100A12 (calgranulin C) in the human OA chondrocytes, whereas S100A8 (calgranulin A) and A9 (calgranulin B) within synovium, chondrocytes and bone (Zreiqatet *et al*., 2007). Furthermore, S100 was suggested as a trigger of catabolic biochemical reactions in OA chondrocytes (Schelbergen *et al*., 2012). In RA subjects, S100 overexpression was found in the synovial membrane stimulating a local release of matrix metalloproteinases (Senolt *et al*., 2006). In our study, we did not find significant correlations between B19V and S100 expression.

We recognise limitations of our study, including a small number of OA cases, semiquantitative measures of immunoexpression, and the lack of clinical data regarding the first-onset manifestations, exacerbations and the appropriate laboratory analyses. However, we believe that the study showed a significant association between B19V DNA detection and IHC staining in synovial tissue, providing new insights into biology and pathogenesis of OA.

In conclusion, our findings suggest that the synovial membrane, an essential organ maintaining homeostasis of the joint cavity, is implicated in the development of OA. Further studies deciphering peculiarities of the structure and function of the inflamed synovium and role of the infectious agents in virus-mediated arthritis are needed.

The author declares that there is no conflict of interest.

ACKNOWLEDGMENTS

This study was supported by the National Research Programme Biomedicine for the Public Health (BIOMEDICINE), project 7.2 and the Latvian Council of Science, project [Interdisciplinary study of inflammatory joint disease-associated influence on neurocognitive function], project No. lzp-2018/1-0149. Finally, the authors would like to thank the Roche Academy for providing the study reagents.

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Received 3 January 2019
Accepted in the final form 5 March 2019

SINOVĪTS OSTEOARTRĪTA PACIENTIEM: MORFOLOĢISKIE UN VIROLOĢISKIE PIERĀDĪJUMI TĀ IETEKMEI UZ SLIMĪBAS ATTĪSTĪBU

Iekaisuma nozīme locītavu deģenerācijas attīstībā osteoartrīta (OA) gadījumā nav pilnībā izzināta. Jaunākie dati liecina, ka procesi, kas veicina iekaisuma izraisītus bojājumus sinoviālās membrānas audos, var būt saistīti ar slimības attīstību. Pētījumā tika analizētas morfoloģiskās izmaiņas sinoviālās membrānas audos OA un reimatoīdā artrīta (RA) pacientiem, kā arī izvērtēta to korelācija ar imūnhistoķīmiski noteiktu cilvēka parvovīrusa B19 (B19V) antigēnu klātbūtni sinoviālo audu paraugos. CD68, S100 un B19 VP1/VP2 antigēnu imūnekspresija sinovija audos tika pētīta, izmantojot rutīnas un dubultās iezīmēšanas imūnhistoķīmijas metodes. OA (28.2%) un RA (28.6%) pacientiem tika novērota B19V antigēnu ekspresija sinoviālajā membrānā. Pētījumā tika novērota pozitīva korelācija starp B19V pozitīvajām endoteliālajām šūnām un sinoviālās membrānas stromālās daļas B19V pozitīvajiem limfocītiem, makrofāgiem, kā arī sinoviocītiem. Korelācija starp sinoviālo audu iekaisuma pakāpi un S100 ekspresiju, kā arī starp B19V ekspresiju un iekaisuma pakāpi netika atrasta. Pētījuma rezultāti liecina, ka sinoviālā membrāna uztur locītavas homeostāzi, un B19V infekcijas izraisīts sinoviālo audu iekaisums ir saistīts ar artrīta attīstību.