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Brief Communication

What does power Doppler signal indicate in rheumatoid synovitis? A point of view from synovial histopathology

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Abstract

To clarify the nature of power Doppler (PD) signals in rheumatoid synovium and to establish the connection between PD signals and active inflammation using synovial histopathology. Ten adult patients (median age 57.0 years, 9 women and one man) with rheumatoid arthritis (RA) were enrolled and received ultrasound (US) examinations. US-guided synovial biopsies using core needle were performed in 7 knees, 2 wrists and one elbow. Each patient had one joint biopsied. In total, 11 synovial specimens were obtained for hematoxylin and eosin staining and histopathologic examinations. The US examinations revealed prominent synovial hypertrophy in all biopsied joints. Six synovial specimens were PD-positive (from 3 knees, 2 wrists and 1 elbow) while 5 synovial specimens were PD-negative (from 5 knees). In comparison with the PD-negative synovial specimens, the PD-positive synovial specimens had significantly more lymphocyte infiltration, vessel proliferation and lining hyperplasia on histologic examination. There was no significant difference in fibrin exudate and stromal fibrosis between the PD-positive and the PD-negative synovial specimens. PD signals in rheumatoid synovium indicate active inflammation and vascularization supported by synovial histopathology. Our study establishes the connection between synovial PD signals and active synovitis in RA.

Keywords: Histopathology; Power Doppler; Rheumatoid arthritis; Synovitis; Ultrasound

1. Introduction

Ultrasound (US) is a useful tool for assessment of rheumatoid arthritis (RA) and has been widely applied in clinical practice. Power Doppler (PD) US detects the vascularity of synovium, which, if it presents, is presumed to result from active inflammation.[1] However, there is a lack of direct evidence supporting the connection between PD signals and active inflammation. PD signals could only indicate increased blood flow according to the physical characteristics of PD. Whether increased blood flow is equivalent to active inflammation remains a question. Several hyperemic conditions, such as penetrating vessels and hypervascular synovial tumor, mimic true synovitis on PDUS imaging. The aim of our study was to clarify the nature of PD signals in synovium and to establish the connection between PD signals and active inflammation in rheumatoid arthritis using analysis of synovial histopathology.

2. Methods

This study was approved by our Institutional Review Board (IRB TCVGH No: CE13214). Ten adult patients (median age

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57.0 years, interquartile range 41.0−61.5 years; 9 women and one man) matching the 2010 American College of Rheumatology/European League Against Rheumatism classification criteria for RA were enrolled.[2] The patients received PDUS examinations (GE LOQIC E9, linear probe with 15 MHz, pulse repetition frequency 0.8 KHz) with standard scanning techniques for swollen joints.[3] US findings of synovial hypertrophy, effusion and synovial PD signals were recorded, and semiquantitatively scored (0−3) according to the Outcome Measurements for Rheumatoid Arthritis Clinical Trials (OMERACT) criteria.[4] The synovial tissues were obtained by US-guided biopsy using a SuperCore biopsy instrument.[5] The PDUS examinations and US-guided synovial biopsies were performed by the authors Lai K-L and Chen H-H, who had 9 and 12 years of US experience, respectively. Each patient had one joint biopsied. The biopsied joints included 7 knees, 2 wrists and one elbow. Each joint provided one synovial specimen, except for a knee joint of a 30-year-old woman, which provided 2 synovial specimens which were located at separate sites with difference in vascularity (Fig. 1).

A total of 11 synovial specimens were obtained for hematoxylin and eosin staining and analysis including stromal lymphocyte infiltration, vessels, fibrin exudate, fibrosis and lining hyperplasia (Fig. 2). The degree of lymphocyte infiltration and fibrosis were semiquantitatively scored using 0−3 according to a modified Rooney's scoring.[6] The scoring of lymphocyte infiltration in stroma was based on the percentage of diffuse lymphocytes per high power field: score 3: >70%, score 2: 30−70%, score 1: <30%, and score 0: absent. The scoring of stromal fibrosis was based on the percentage of fibrosis in stroma: score 3: >50%, score 2: 25−50%, score 1: <25%, and score 0: absent. The interpretation of synovial histopathologic findings was performed by the author Wen M-C. The association of PD signals with synovial histopathologic findings was assessed. Quantitative variables were expressed as the mean ± standard deviation and compared using Mann−Whitney U test. Qualitative variables were compared using Fisher's exact test. A p-value <0.05 was considered statistically significant.

3. Results

The US examinations revealed prominent synovial hypertrophy grade 3 in all biopsied joints, and presence of synovial effusion in 3 knee joints. Six synovial specimens were obtained from the synovial sites where PD signals presented (in 3 knees, 2 wrists and one elbow), while 5 synovial specimens were obtained from the synovial sites where no PD signals presented (in 5 knees). In comparison with the PD-negative synovial specimens, the PD-positive synovial specimens had significantly more lymphocyte infiltration in stroma (score 2.7 ± 0.5 vs. 0.6 ± 0.5, $p < 0.001$), significantly greater presence of vessels (100% vs. 20%, $p < 0.05$) and significantly greater presence of lining hyperplasia (83.3% vs. 0%, $p < 0.05$) on histologic examination. Three (60%) PD-negative synovial specimens had score 1 lymphocyte infiltration that demonstrated the presence of minor inflammation in the hypertrophied synovium even without PD signals. There was no significant difference in fibrin exudate (16.7% vs. 40%, $p = 0.42$) or stromal fibrosis (score 1.3 ± 1.2 vs. 1.6 ± 0.9, $p = 0.68$) between the PD-positive and the PD-negative synovial specimens (Table 1).

4. Discussion

RA is an autoimmune disorder with clinical manifestations of chronic synovitis, pannus formation, cartilage destruction and bone erosion. The characteristic histopathologic findings of RA synovium include (1) synovial lining hypertrophy, (2) diffuse infiltration of lymphocytes and plasma cells in the stroma, (3) marked proliferation of blood vessels, (4) proliferation of granulation tissue usually accompanied by fibrin deposition or fibrinoid necrosis, and (5) hemosiderosis in the synovium.[7] PDUS is a useful tool for assessment of joint inflammation. In RA patients, both synovial hypertrophy and synovial vascularity can be easily detected and semiquantitatively scored by PDUS.[8] But the presence of synovial PD signals is not a specific sign for RA, and may be seen in non-RA conditions such as septic arthritis and crystal-induced arthritis.[9]

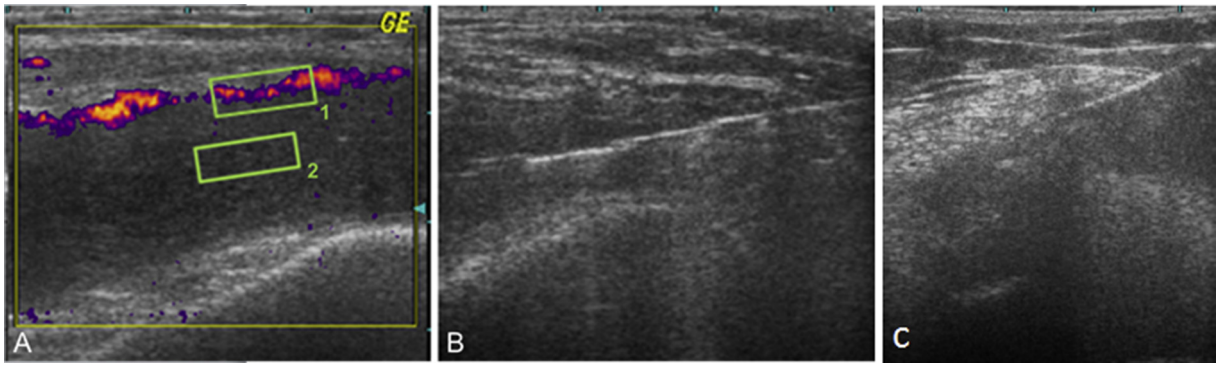

Fig. 1. Power Doppler ultrasound of left knee joint in a 30-year-old woman with rheumatoid arthritis. (A) Transverse scan at the suprapatellar area revealed prominent synovial hypertrophy. Presence of power Doppler signals at the basal layer of synovium (block 1). Otherwise, no synovial power Doppler signal elsewhere (block 2). (B) Ultrasound-guided biopsy of synovium in the block 2 area. (C) Ultrasound-guided biopsy of synovium in the block 1 area.

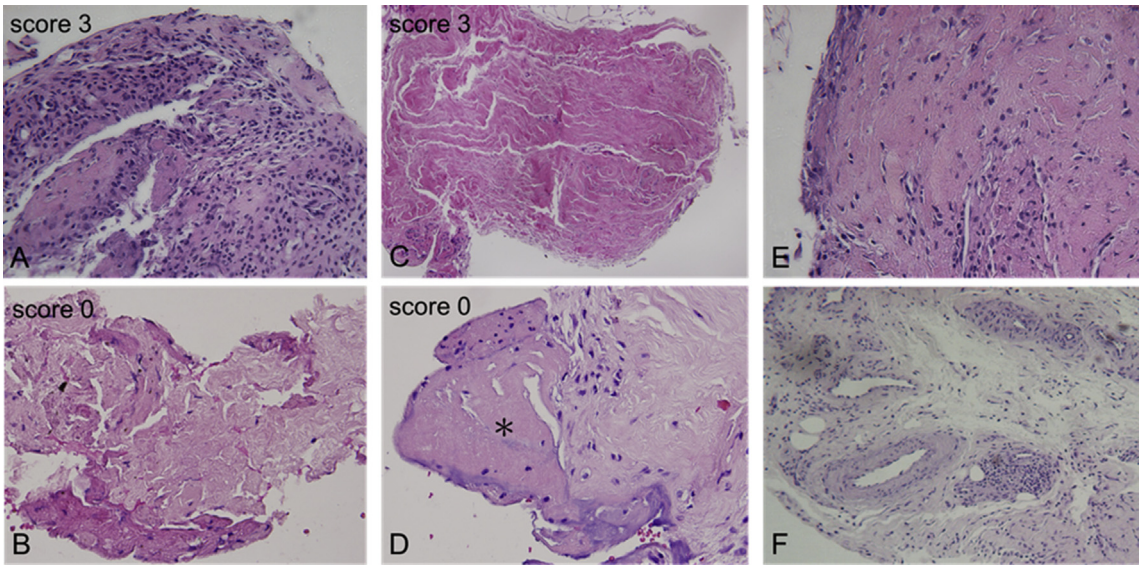

Fig. 2. Histopathology of synovium in rheumatoid arthritis (HE stain, 400×). (A) Massive lymphocyte infiltration in the stroma, and (B) absence of lymphocyte infiltration [diffuse infiltrates of lymphocyte score 3: >70%, score 2: 30−70%, score 1: <30%, score 0: absent]. (C) Massive fibrosis (dense fibers) of synovium, and (D) no fibrosis [fibrosis score 3: >50%, score 2: 25−50%, score 1: <25%, score 0: absent] (* represents fibrin exudate). (E) Lining hyperplasia. (F) Vessels in the stroma represent vascularization and pannus.

Table 1
Correlation between power Doppler signals and synovial histopathology in rheumatoid arthritis.

	PD+ specimens (n = 6)	PD− specimens (n = 5)	*p* value
Lymphocyte infiltration score (0−3)	2.7 ± 0.5	0.6 ± 0.5	<0.001
Vessels (n. positive (%))	6 (100)	1 (20)	<0.05
Fibrin exudate (n. positive (%))	1 (16.7)	2 (40)	0.42
Stromal fibrosis score (0−3)	1.3 ± 1.2	1.6 ± 0.9	0.68
Lining hyperplasia (n. positive (%))	5 (83.3)	0 (0)	<0.05

Quantitative variables are presented as mean ± standard deviation. PD = power Doppler signals.

The presence of PD signals in the synovium represents the status of increased blood flow, and is presumed to be active inflammation. However, there is a lack of direct evidence supporting the connection between PD signals and active inflammation. Traditionally, synovial tissue is obtained by arthroscopic biopsy; investigators then compare the synovial histology with the preoperative PDUS images.[10] With arthroscopic biopsy technique, it is difficult to ensure that the section of synovium specimen and the location of synovial PD signals are on the same plane, so the synovial histology cannot be correlated with the preoperative PDUS images. In 2006, Koski et al. proposed an alternative method of synovial biopsy using portal and forceps with US guidance.[11] With this real-time US-guided biopsy technique, investigators could ensure that the synovial tissue was obtained from the site of PD signals existence, so the synovial histology could be correlated with the real-time PDUS images. In our study, US-guided core needle biopsy of synovium was adopted to research the nature of synovial PD signals in RA patients.

Our results showed significantly more lymphocyte infiltration, vessel proliferation and synovial lining hypertrophy in PD-positive synovium. These histopathologic findings provided direct evidence of active inflammation, and established the connection between synovial PD signals and active synovitis. Notably, three (60%) PD-negative synovial specimens had score 1 lymphocyte infiltration that demonstrated the presence of minor inflammation in the hypertrophied synovium even without PD signals. Minor synovitis may not generate PD signals due to being below the lower limit of PD detection sensitivity based on the quality of the US machine. Our results were consistent with the data reported by Koski et al.[12] Our data interpretation was limited due to small case number, so further large study would be required to clarify the correlation between PD signal intensity and the degree of synovial inflammation.

In conclusion, PD signals in rheumatoid synovium indicate active inflammation and vascularization, supported by the histopathologic evidence of significantly more lymphocyte infiltration, vessel proliferation and lining hyperplasia. Our study establishes a connection between synovial PD signals and active synovitis in RA.

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